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REYE'S SYNDROME

HEARINGS

BEFORE THE

SUBCOMMITTEE ON NATURAL RESOURCES,
AGRICULTURE RESEARCH AND ENVIRONMENT

OF THE

COMMITTEE ON

SCIENCE AND TECHNOLOGY

U.S. HOUSE OF REPRESENTATIVES

NINETY-SEVENTH CONGRESS

SECOND SESSION

SEPTEMBER 17 AND 29, 1982

[No. 178]

Printed for the use of the
Committee on Science and Technology



U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON : 1983

20-517 O

H701-6

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Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, Department of Health and Human Services, accompanied by Harry M. Meyer, Jr., M.D., Director, National Center for Drugs and Biologics, Food and Drug Administration; Walter R. Dowdle, Ph. D., Director, Center for Infec- tious Diseases, Centers for Disease Control; Gerald Quinnan, M.D., Director, Division of Virology, National Center for Drugs and Biologics, and Eugene Hurwitz, M.D.....	82
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REYE'S SYNDROME

FRIDAY, SEPTEMBER 17, 1982

HOUSE OF REPRESENTATIVES, COMMITTEE ON SCIENCE AND
TECHNOLOGY, SUBCOMMITTEE ON NATURAL RESOURCES,
AGRICULTURE RESEARCH AND ENVIRONMENT,

Washington, D.C.

The subcommittee met, pursuant to call, at 9:45 a.m., in room 2318, Rayburn House Office Building, Hon. James H. Scheuer (chairman of the subcommittee) presiding.

Mr. SCHEUER. The Subcommittee on Natural Resources, Agriculture Research and Development will now come to order.

We meet this morning to consider an important subject which has enormous ramifications for America's public health, and particularly for the public health of our children. I speak of course about the controversy surrounding the alleged association of Reye's syndrome and the use of aspirin. The matter we speak about is somewhat emotionally charged, because the question of the health of our children is a very emotional commitment that most of us have, and we all want to proceed with great caution and do everything possible to assure their well-being.

Speaking as a parent of four kids, I can say that nothing is more agonizing than when sickness hits our children and when our kids become ill, even if it is comparatively benign and not a terribly threatening illness. As parents we are deeply and emotionally involved. So it is terribly important in these decisions when a child is ill for parents to have adequate guidance in how to treat the child's disease, particularly in administering drugs and medications.

No medication has been longer used than aspirin. It is a staple in everyone's medicine cabinet. My 87-year-old mother raised five very happy and healthy kids, quite successful kids based on two nostrums. If it hurt on the outside, rub Vaseline on it. If it hurt on the inside, pop in a few aspirin. This modality of treatment started about 65 years ago with my older brother and continued through 20 years for five Scheuers, and here we are moderately successful. So aspirin has played a large part in my life and in the life of my kids.

Now the Department of Health and Human Services has told the public that an association exists between this drug that they have successfully used for decades, maybe for generations, and the much-feared Reye's syndrome, a rare but sometimes lethal illness affecting young children. Shortly after the Department of Health and Human Services began these warnings, physicians around the country began contacting me by the hundreds, phone calls and let-

ters asking that our committee conduct some kind of an investigation.

Almost unanimously they claimed that the Department had acted prematurely, some said precipitously, in taking action so quickly, with little attention being paid to the available scientific facts and to the quality of the scientific investigation. With such charges and with the deep concern that had been raised so widely from so many scientific quarters, I felt that nothing less than a full inquiry by this subcommittee and today's hearing was called for.

We are going to hear from a number of very distinguished witnesses who have worked firsthand with Reye's syndrome. In fact, one of the witnesses, Dr. George Johnson, actually discovered and identified the disease in the United States. And we are going to hear of their great concerns about the way in which HHS has acted in this matter.

Now, Dr. Edward Brandt, the Assistant Secretary of HHS for Health, was scheduled to testify at this hearing. In fact, his testimony was hand-delivered up to us late yesterday. However, last night we received word that unless Dr. Brandt was to be scheduled the very first witness on this morning's hearing that he would refuse to testify at all. We were astonished and nonplussed at this message. Obviously it was unacceptable to the subcommittee, and Dr. Brandt will appear here, hopefully next week, if that is convenient to him, but he will appear, either by invitation or by subpoena, so that we can have the advantage of the Department's views on Reye's syndrome and the actions that they have taken. He will then have the opportunity to answer some searching questions that this subcommittee will put to him which he is either unprepared or unwilling to answer today.

Ironically, I might say it was just a year ago in connection with another hearing that Dr. Brandt was scheduled to testify before this committee. At that time we had the witness, but no testimony. Today we have the testimony, but no witness. We succeeded a year later in getting him and his testimony together in time and space. It took us a couple of weeks, but he did come back with his testimony, and we hope this year to achieve the same felicitous result of getting Dr. Brandt and his testimony together again in time and space before this committee to answer questions.

Apparently he loves us not wisely, but too well. He enjoys his twofer, two for the price of one, two appearances where he has time between the first and second appearance to do his homework. We welcome that. We had two successful encounters with him last year, and we have his testimony today and we hope to have him together with his testimony sometime next week.

[The opening statement of Hon. James H. Scheuer follows:]

OPENING STATEMENT
HONORABLE JAMES H. SCHEUER
SEPTEMBER 17, 1982

THE SUBCOMMITTEE WILL COME
TO ORDER.

WE MEET THIS MORNING TO CONSIDER
AN IMPORTANT SUBJECT WHICH
HAS ENORMOUS RAMIFICATIONS
FOR AMERICA'S PUBLIC HEALTH.

I SPEAK OF COURSE OF THE CONTROVERSY
SURROUNDING THE ALLEGED ASSOCIATION
BETWEEN ASPIRIN USE AND REYE'S
SYNDROME.

THE MATTER WE CONSIDER IS AN
EMOTIONALLY CHARGED ONE.

CERTAINLY WHEN THE HEALTH AND
SAFETY OF OUR OFFSPRING
ARE INVOLVED, WE WANT TO
PROCEED WITH GREAT CAUTION
AND DO EVERYTHING POSSIBLE
TO ASSURE THEIR WELL-BEING.

FROM A PERSONAL EXPERIENCE, I CAN
RELATE, AS I'M SURE ALL
PARENTS CAN, THAT NOTHING
IS MORE AGONIZING THAN
WHEN A CHILD BECOMES ILL,
EVEN WITH THE MOST COMMON
OF DISEASES.

IT IS IMPORTANT IN THOSE
DIFFICULT SITUATIONS THAT
PARENTS HAVE GUIDANCE AS
TO HOW TO TREAT THEIR
CHILD'S ILLNESS, PARTICULARLY
WHEN IT COMES TO THE USE OF
MEDICATIONS.

AND NO MEDICATION IS MORE WIDELY KNOWN
AND USED THAN ASPIRIN, WHICH
IS PRETTY MUCH A STAPLE IN EVERY-
ONE'S MEDICINE CABINET.

WORLDWIDE, IN FACT, HUNDREDS OF
MILLIONS OF DOSES OF
ASPIRIN ARE ADMINISTERED
TO CHILDREN DAILY, AND
80% OF CHILDREN'S
ASPIRIN IS PURCHASED TO
TREAT SYMPTOMS OF FLU AND
OTHER VIRUSES.

SUDDENLY, THE DEPARTMENT OF
HEALTH AND SERVICES HAS TOLD
THE PUBLIC THAT AN ASSOCIATION
EXISTS BETWEEN THIS DRUG THEY
HAVE USED SUCCESSFULLY FOR DECADES
AND THE MUCH FEARED REYE'S SYNDROME,
A RARE BUT OFTEN LETHAL DISEASE
AFFECTING YOUNG CHILDREN.

SHORTLY AFTER THE DEPARTMENT OF HEALTH
AND HUMAN SERVICES (HHS) BEGAN
ITS WARNINGS, HUNDREDS OF
PHYSICIANS FROM ACROSS THE COUNTRY
BEGAN WRITING TO ME TO ASK THAT
AN INVESTIGATION BE CONDUCTED.

ALMOST UNIFORMLY THEY CLAIMED
THAT THE DEPARTMENT HAD ACTED
PRECIPITIOUSLY, WITH LITTLE
ATTENTION BEING PAID TO
SCIENTIFIC FACTS AND QUALITY.

WITH SUCH CHARGES, THE PUBLIC
INTEREST DEMANDED NO LESS
THAN A FULL SUBCOMMITTEE
INQUIRY AND TODAY'S HEARING
REPRESENTS THE CULMINATION
OF THAT EFFORT.

WE ARE GOING TO HEAR FROM A
NUMBER OF VERY DISTINGUISHED

WITNESSES WHO HAVE WORKED
FIRST HAND WITH REYE'S
SYNDROME.

IN FACT, ONE OF THE WITNESSES,
DR. GEORGE JOHNSON,
ACTUALLY DISCOVERED THE
DISEASE IN THE U.S.

WE ARE GOING TO HEAR OF
THEIR GREAT CONCERNS
WITH THE WAY HHS HAS ACTED
IN THIS MATTER.

DR. EDWARD BRANDT, ASSISTANT
SECRETARY OF HHS FOR
HEALTH WAS SUPPOSED TO
TESTIFY AT TODAY'S HEARING.

WE HAD GOTTEN A LETTER FROM
HHS INDICATING THAT HE
WOULD TESTIFY AND WE
EVEN RECEIVED HIS TESTIMONY
LATER YESTERDAY.

LAST NIGHT WE RECEIVED WORD THAT
UNLESS DR. BRANDT WAS TO BE THE
VERY FIRST WITNESS, HE WOULD
REFUSE TO TESTIFY AT ALL.

OBVIOUSLY THIS IS UNACCEPTABLE TO
THE SUBCOMMITTEE, AND EITHER
THROUGH ANOTHER INVITATION, OR
SUPEONA, DR. BRANDT WILL
PRESENT THE DEPARTMENT'S VIEWS ON
REYE'S SYNDROME, HOPEFULLY NEXT
WEEK IF THIS IS CONVENIENT
TO HIM.

HE WILL THEN HAVE THE OPPORTUNITY TO ANSWER
SOME SEARCHING QUESTIONS FROM
THE SUBCOMMITTEE, WHICH
APPARENTLY HE IS UNPREPARED OR
UNWILLING TO ANSWER TODAY.

IRONICALLY, IT WAS EXACTLY A
YEAR AGO THAT DR. BRANDT JUST
APPEARED BEFORE THE
SUBCOMMITTEE.

AT THAT TIME HE HAD NOT
SUBMITTED TESTIMONY.

TODAY WE DO HAVE HIS TESTIMONY,
BUT WE DON'T HAVE HIM.

IN THE NEAR FUTURE WE HOPE TO
ACHIEVE A FIRST HERE AT
THE SUBCOMMITTEE, TO HAVE
DR. BRANDT AND HIS TESTIMONY
ALL AT ONE TIME.

BEFORE WE COMMENCE, I WOULD
LIKE TO RECOGNIZE _____,
A VALUED MEMBER OF THE
SUBCOMMITTEE, FOR SOME
BRIEF OPENING REMARKS.

* * * * *

WITHOUT FURTHER ADIEU, I
WILL NOW CALL OUR
FIRST WITNESS, I

Mr. SCHEUER. Without any further ado, we will call the first witness this morning, Dr. George Johnson, a very distinguished pediatrician from Fargo, N. Dak., who incidentally was the discoverer and the identifier of Reye's syndrome in this country. We are delighted to have you with us, Dr. Johnson. We have enjoyed your testimony, and we suggest you take 10 or 12 minutes informally to review the highlights of your testimony and anything else that comes to mind, and then I am sure we will have some questions for you.

**STATEMENT OF DR. GEORGE JOHNSON, PEDIATRICIAN,
FARGO, N. DAK.**

Dr. JOHNSON. Thank you, Mr. Chairman. It might be of interest to the gathering to know a bit of the history surrounding Reye's syndrome in America. I first became enmeshed with this mysterious disease of children almost 20 years ago, in 1962, when I served a stint as a young epidemiologist at the North Carolina State Health Department.

Mr. SCHEUER. Excuse me. Would you turn on the mike and pull it closer to you?

Dr. JOHNSON. I think I will begin again, Mr. Chairman.

It is my privilege to be here this morning. I thought it appropriate to review a bit of the history of Reye's syndrome in America as a background for this hearing. I first became enmeshed in the mysteries of this new disease of childhood in 1962, almost 20 years ago, when I served a stint as a young epidemiologist at the North Carolina State Health Department. Coincident with an influenza B epidemic there were 16 cases of sudden death in children scattered throughout the State. Remarkable brain encephalopathy and fatty degeneration of the visceral organs, especially the liver, seemed to be the hallmark of this disease.

I would like to provide a brief description of the first case of Reye's syndrome described in the United States, which appeared in March 1962 at the White Memorial Hospital in Charlotte, N.C. The pediatrician's notes stated that this was a 10-year-old child with a cough, fever, runny nose for several days. The 10-year-old girl seemed to get better and then began an episode of steady vomiting, and within a short period of time that child had been given three suppositories for vomiting, Compazine. The child rapidly developed a coma consequent to the vomiting. The pediatrician noted that this was a well-developed, well-nourished child, and she was comatose. Her pupils were dilated, she had a slight inflammation of the throat, and an irregular respiration. Her liver appeared to be slightly enlarged, and she had upgoing toe signs on her neurologic examination, the progressive stages of Reye's syndrome, twitching of muscle groups, and the doctor's impression was that he was dealing with an unknown disease.

He could not make a diagnosis. He knew that she had a flu-like illness, a respiratory infection. He recommended that further investigation be done into the drugs she might have taken, into the possible toxic exposure she might have had. He worried about the possibility of encephalitis, because he knew there was influenza in the community at that time, and he knew that could follow that

type of illness. However, the child died in a very short period of time.

At the postmortem the pathologist was impressed by the remarkable brain swelling, cerebral edema, and the enlarged fatty liver, as well as fatty changes in other organs. He noted peculiar fatty changes in the liver, kidney, and heart. Of course, these findings have been corroborated and studied at great length ever since this first unfortunate case of Reye's syndrome.

After investigating the case, there was a rapid succession of subsequent cases. I believed at that time and I still do believe that we dealt with a new disease. We are dealing with a new disease that was not present before the 1950s or the 1960s either in Australia or in the United States. And during this interval, Dr. Reye in Australia made his climinal description of what is known as Reye's syndrome. This was a pathological correlation in 20 children published in 1963. This disease was first thought to be very rare. It was called encephalopathy, but now we know it occurs regularly in the United States, and has occurred regularly coincident with influenza B epidemics ever since the first epidemic that we investigated in North Carolina in 1962.

Our group made the first association between this disease and the appearance of influenza B in schoolage children. The CDC says there are at least 600 to 1,200 cases in this country each year. There are perhaps many more mild cases, and we have much to learn about the milder forms of Reye's syndrome. The excellent description in a prospective study in Michigan pointed out there are perhaps as many advanced stages of Reye's syndrome as there were cases of measles encephalitis before we had a measles vaccine.

The close association between influenza B in children and Reye's syndrome has persisted since 1962. Dr. John Partin has stated that influenza B has been and still is the main inciting factor in the onset of Reye's syndrome. However, as you all know, about 10 percent of the cases of Reye's syndrome follow the onset of pernicious vomiting and the development of varicella, so there is close association with chickenpox as well. Reye's syndrome has also occasionally been associated with other viruses such as parainfluenza, Coxsackie virus, adenovirus, infectious mononucleosis, and others. Dr. Crocker from Nova Scotia—he is here this morning, I believe—has studied an emulsifier in a spruce budworm spray that he feels may be associated.

The anticonvulsive drug, valproic acid, has also been shown to give a syndrome similar to Reye's syndrome. There are fungal toxins which are noted in Thailand and they have been implicated in the Udorn province in causing a disease very similar to the disease we see in the United States. Eating of an unripe fruit in Jamaica called the akee [phonetic] fruit has also been shown to give a syndrome similar to Reye's. Of course, now we have the association between aspirin and Reye's syndrome. Aspirin has been called a factor in the development of the disease—at least that is the hypothesis. I mentioned the foregoing things to set the stage for the main topic of this particular hearing, and that is just what might be the culpability of acetylsalicylic acid in the events leading up to Reye's syndrome.

Mr. SCHEUER. That is the major ingredient in aspirin?

Dr. JOHNSON. That is aspirin, Mr. Chairman. I certainly cannot answer this question. As a general practitioner of pediatrics, I have not been privy to the raw data developed. However, from what I know from reading my journal, I do not think anyone can answer those questions. I come from a group of 12 busy, active pediatricians. We communicate closely. We practice in a regional medical center in Fargo, N. Dak., and we can only say simply that none of us has seen clinical association as general practicing pediatricians between Reye's syndrome and the ingestion of aspirin.

After repeated national broadcasts of this purported association, in the past months I have received more phone calls and queries from parents about this single issue than about anything else in my practice. They want to know what about this bad disease that aspirin causes. They ask about this much more than they ask about colic, diarrhea, and colds.

Mr. Chairman, believe me, that is a lot of telephone calls. When we recommend aspirin over the telephone to a mother that has called in, a mother that is worried about her child, the sort of thing that you mentioned in your opening statement, we often hear a diminuendo in her voice, you are recommending aspirin, doctor? I thought aspirin was not the thing that my child should have. So in effect this warning against the use of aspirin in influenza, to my way of thinking and to my partners', seems to be a warning against the use of aspirin with any child. I would like to emphasize that.

As practitioners we have all read the reports of the committee on infectious disease of the American Academy of Pediatrics in the June issue and the rebuttal. None of us have been privy to the details of the methodology, and I do not think any of us would be qualified to examine the raw data from these studies. That is for the scientists. However, we do know that the Arizona, Michigan, and particularly the Ohio studies making this relationship have been strongly criticized because of lack of careful matching of the severity of the prodromal illness in both the cases and the controls. These studies also were retrospective surveys. I am sure many of the other witnesses will point that out.

How many of us, I would ask as a practicing pediatrician, can remember the medications we gave our children 10 to 12 days before, considering the multiple-shelf medications all of us have in our household. Also in our practice, and I dare say most practices of general pediatricians, the vast majority of mothers call Tylenol, which is the most commonly used form of the antipyretic acetaminophen, they call it liquid aspirin. It is not. Support for this lack of ingredient awareness was provided by Wilson, noting that up to 25 percent of febrile children who are historically positive by recall for aspirin or acetaminophen have serum levels of the opposite drug. This would certainly be corroborated by my own experience in private practice.

We are also told that the Ohio study made no ascertainment of the association between aspirin and Reye's syndrome—made no ascertainment of viral diagnosis in the controls. Was, therefore, the illness in the cases and the illness in the controls really the same viral agent? As a firing line pediatrician, I can say that I know firsthand that there is often a multiplicity of other viral agents

present in a community even when there is an epidemic of influenza. We are also aware in the past of previous associations such as the association between normal lactation and breast cancer, the purported association between prenatal irradiation and childhood leukemia, tonsillectomy, and Hodgkin's disease, that have never been proven. I wonder if there is something of the same in the association between aspirin and Reye's syndrome.

Three general pediatricians spoke before the recent National Reye's Syndrome Foundation meeting in Tampa, Fla., and they voiced remarkably similar concerns to those that I have just tried to outline. Massive inquiry by the public at the present time I think makes this a hot issue.

I am also concerned, in closing, about one other facet of this association between aspirin and Reye's syndrome that I think has been scarcely mentioned. Will the clamor given this tenuous association divert the public and indeed divert practicing physicians from the urgent tasks of future research regarding this puzzling entity? Will they assume that the answer has been found, that there is an association between aspirin and Reye's syndrome? The National Institutes of Health consensus committee on Reye's syndrome in March of 1981 outlined some of the research needs, and I would like to mention them. We need better demographic data with regard to Reye's syndrome, why the relatively low incidence, why the seasonal incidence?

Mr. SCHEUER. The what incidence?

Dr. JOHNSON. The apparent seasonal incidence, the wintertime incidence. Why the apparent geographical maldistribution? We see relatively little Reye's syndrome in our part of the country. There is a fair amount in southern Minnesota. Why does that occur? I do not think it is lack of casefinding, at least in our area.

There is further research needed on the etiology of Reye's syndrome. The specificity of screening tests for the original diagnosis, so important to the child developing Reye's syndrome. The most effective treatment in monitoring procedures during the hospital care of the child is in need of additional research. And of course the long-term sequellae in Reye's syndrome in children who have had the disease needs additional moneys and research.

I would like to offer a couple of other suggestions that were not made by the consensus committee of the NIH. We now have adequate, increasingly sophisticated methods of managing this difficult problem even in the late stages. It remains true, however, that immediate diagnosis and efficacious treatment is what lowers the morbidity and mortality for children with Reye's syndrome. It seems since this is largely a disease of rural-dwelling school-age children that we need to have information in every hospital in America no matter how small that accepts these kinds of children as emergency patients. We need to have information about Reye's syndrome in these hospitals.

We need to form multidisciplinary groups to evaluate and cooperate in new methods of treatment for Reye's syndrome. These treatment centers must have tertiary capabilities and need to be identified and listed for each region. I think we have an excellent model already in the establishment of newborn intensive care

units, and we might be able to follow that approach with Reye's syndrome.

I do not think we have had in the past and I think we desperately need a continuing effort in the Bureau of State Services at CDC to encourage territorial health officers to make this disease a priority item in their daily work. We need reporting on a State-by-State basis for better demographic data, and perhaps the State epidemiologists could identify the problems for the physicians in their State, thereby enhancing physician interest.

There are many things that need to be done in the investigation of Reye's syndrome in the future. As a general practitioner of pediatrics, it is my opinion that we have invoked the jury before thoroughly evaluating all the evidence of Reye's syndrome, and therefore I believe at the present time that a label on aspirin as a means of preventing or reducing morbidity and mortality in Reye's syndrome is unwarranted.

I appreciate the privilege to come to Washington to see my son, who is working for Congressman Dorgan, and to see the sunshine on the Capitol this morning. It reminded me of the mountains out west.

Thank you.

[The prepared statement of Dr. Johnson follows:]

TESTIMONY -- REYE'S SYNDROME

Subcommittee on Natural Resources, Agriculture Research & Environment

Mr. Chairman, Distinguished Members, I am George Magnus Johnson, M.D., pediatrician, Fargo Clinic, Fargo, North Dakota. I first became enmeshed in the mysteries of a sudden devastating illness affecting children in 1962, during a stint as a young epidemiologist assigned by the Epidemic Intelligence Service (EIS) to the North Carolina State Department of Health. Coincident with an influenza B epidemic, sixteen cases of sudden death in rural dwelling school age children were noted during a three month period. Remarkable brain swelling (encephalopathy), fatty degeneration of the liver and other visceral organs seemed to be hallmarks of the pathologic findings. A brief description of the first case at the Charlotte, North Carolina, Memorial Hospital during March, 1962 illustrates the typical clinical course and pathologic findings of Reye's Syndrome.

The pediatrician's notes at that time said, "A ten-year-old with upper respiratory illness characterized by fever, cough and rhinitis for several days, treated with Terramycin and symptomatic measures such as rest. During the 24 hours prior to admission the child received three suppositories for vomiting, Compazine. The child was admitted because of rapidly developing coma."

The pediatrician went on to note that this was a well developed, well nourished child who was comatose. Her pupils were dilated, reacting somewhat sluggishly to light. There was slight inflammation of her throat.

Her neck was supple; no neck stiffness was noted. Rapid respirations, 40 to 44 per minute, were seen and her liver appeared to be slightly enlarged. On neurologic examination she had bilateral upgoing toe signs. Occasionally chronic twitching of single muscle groups, such as in the right arm or left leg, was seen.

The doctor's impression after examination of the first case investigated in the United States was 1) upper respiratory disease, 2) acidosis and dehydration, 3) coma of unexplained etiology. He felt that he could not make a definitive diagnosis and recommended that the child be followed closely. He noted that there was no history of exposure to undetermined drugs or accidental ingestion of drugs. He worried about the possibility of encephalitis as an explanation for the coma, particularly "following as it does on the heels of an influenza-like illness."

At post mortem the pathologist noted 1) marked brain swelling, 2) moderate fatty hepatomegaly, 3) marked basilar pulmonary hyperemia and edema, 4) renal cortical pallor, and 5) clinical influenza with no history of intoxication. The pathologist remarked that the fatty metamorphosis of the liver was characterized by generally small type of diffusely distributed vacuolization. He also noted fatty changes in the kidney and the heart.

After investigating this case and a rapid succession of subsequent cases I believed at that time, and I still believe, that this was an entirely new disease or syndrome involving children. Doctor Douglas Reye of Australia also believed that fact. During this same interval he made his classical

clinical-pathologic correlations in twenty children, all of whom died. Since then, Reye's syndrome--first called encephalopathy and fatty degeneration of the viscera--has occurred regularly in the United States, particularly at the time of influenza B epidemics in rural dwelling school age children--correlations first made by our group in North Carolina. Initially thought to be a rare disease, it is now estimated by CDC that at least 600 to 1200 cases occur each year in this country. Corey's excellent prospective study in Michigan in 1975 estimated an incidence in school age children during influenza B epidemics akin to the incidence of measles encephalitis during an epidemic of that disease prior to the advent of measles vaccine (approximately 1 per 1,000 cases).

The close association between influenza B in children and Reye's Syndrome has persisted since the first flurry of cases in 1962. Doctor John Partin, an eminent researcher in the pathophysiology of Reye's Syndrome, states "influenza B has been and still is the main inciting factor in the onset of Reye's syndrome." About ten percent of the cases follow varicella or chickenpox, with the same sudden onset of pernicious vomiting and rapid onset of coma.

Reye's syndrome has also been occasionally associated with a host of other viruses, especially influenza A, and to a much lesser extent with such viruses as parainfluenza, Coxsackie virus, adenovirus, infectious mononucleosis and others. Doctor Crocker's group in Nova Scotia noticed the possible importance of an emulsifier in a spruce budworm spray as a causative factor. The anticonvulsant drug, valproic acid, can also cause

a syndrome similar to Reye's Syndrome. Fungal toxins called aflatoxins present in spoiled food cause encephalopathy and fatty degeneration of the liver, particularly in Udorn Province of Thailand. Eating of unripe fruit in Jamaica has been known for many years to be the etiology of brain swelling and liver deterioration. And now, of course, aspirin has been studied as a co-factor in the onset of Reye's Syndrome.

The foregoing, then, sets the stage for the main topic of this hearing: Just what is the culpability of acetylsalicylic acid in the cascade of events leading to Reye's Syndrome? I certainly can't answer that question. I don't think anyone can. However, as a group of twelve busy, closely communicating pediatricians practicing in a regional medical center in Fargo, North Dakota, we must simply say none of us has seen clinical evidence of an association between aspirin ingestion and Reye's Syndrome. After repeated national broadcasting of this purported association I do know we have received more phone calls and queries, "what about aspirin causing this bad disease, Doc?" than we have for colic, diarrhea or the ordinary cold. When we recommend aspirin over the phone for a febrile child there is always a doubtful diminuendo in the mother's voice. "Is aspirin really OK--I thought -- ?" We have all noted this even though there has been no varicella or influenza B in our area during recent months. In effect, the warning against the use of aspirin in influenza seems to be a warning against the use of aspirin in any febrile child.

As practitioners we have all read the report of the Committee on Infectious Disease of the American Academy of Pediatrics in the June issue of Pediatrics as well as a rebuttal in the same issue. None of us has been privy to the details of methodology in the studies correlating aspirin ingestion with Reye's Syndrome. I doubt that any of us could properly analyze the raw unpublished data even if available. That is best left to the scientists, but we do know that the Arizona, Michigan and particularly the Ohio studies making this relationship have been strongly criticized because careful matching of the severity of the prodromal illness in cases and controls was not done. These studies, retrospective surveys, were carried out a week or more after medications were given. How many among us, living in households having multiple shelf medications, can remember exactly what/how much we gave our child seven-ten days before? Also, in our practice, the vast majority of mothers call Tylenol the most commonly used form of the antipyretic acetoaminophen, "liquid aspirin." Support for this lack of ingredient awareness has been provided by Wilson who noted that up to 25 percent of febrile children who are historically positive by recall for aspirin or acetoaminophen have serum levels of the opposite drug.

We are also told that the Ohio study made no ascertainment of viral diagnosis in the controls. Was, therefore, the illness in cases and controls caused by a similar viral agent? As "firing line" pediatricians we know first hand the multiplicity of other viral agents present in children even during an epidemic of influenza. We are also aware that the medical literature abounds with conflicting reports relating, for

example, normal lactation and breast cancer, prenatal irradiation and childhood leukemia, tonsillectomy and Hodgkin's disease.

Nor are we alone in our "hunches." At the recent National Reye's Syndrome Foundation meeting in Tampa, Florida, a panel of three experienced general pediatricians voiced remarkably similar concerns about the Surgeon General's advisory on aspirin in Reye's Syndrome. Massive inquiry by the public makes this a "hot," timely subject.

I am also concerned about another facet of this subject that has been scarcely mentioned. Will the clamor given the tenuous association between salicylates and Reye's Syndrome divert the public and many physicians from the urgent tasks of future research regarding this puzzling entity? Will they assume that the answer has been found? The National Institutes of Health Consensus Conference statement on the diagnosis and treatment of Reye's Syndrome, held March 2-4, 1981, scores some of the research needs:

1. Epidemiological-better demographic data. Why the relatively low and seasonal incidence? Why the apparent geographic maldistribution?
2. Further research regarding etiology.
3. The specificity of screening tests for Reye's Syndrome.
4. The most effective treatment and monitoring procedures.
5. The short and long term sequelae of known Reye's Syndrome cases.

In closing, permit me to offer several other suggestions which I believe are paramount in the effort to decrease morbidity and mortality from Reye's Syndrome.

1. We now have adequate, increasingly sophisticated methods of managing this difficult problem, even in the late stages. It remains true, however, that a majority of cases still occur among rural dwelling school age children. Therefore, every hospital in America, no matter how small, that accepts children as emergency patients needs a packet of information on Reye's Syndrome for emergency room display.
2. There is a need for multidisciplinary cooperation in the evaluation and treatment of Reye's Syndrome. Treatment centers with tertiary care capabilities need to be identified and listed for each state. We already have an excellent example to follow in the establishment of newborn intensive care units.
3. A major and continuing effort should be conducted through the Bureau of State Services at CDC to encourage state and territorial epidemiologists to consider Reye's Syndrome a "priority disease and a reportable disease." A biannual report in each state from the epidemiologist to physicians would perhaps do much to increase awareness and accuracy in reporting.

Obviously there are many other needs to be met in our investigation of this tenth leading killer of school age children. As a general pediatric practitioner, it is therefore my opinion that we have invoked the jury before thoroughly evaluating all the evidence and, therefore, I do not feel that a warning label on aspirin as a means to prevent or reduce the amount of Reye's Syndrome in this country is warranted at this time.

I greatly appreciate the invitation to speak before this committee. It has been a special privilege.

Mr. SCHEUER. Thank you very much, Dr. Johnson.

You say that the action calling for labeling by the Department of Health and Human Services is premature. What do you predict will be the result of that action?

Dr. JOHNSON. Well, I think, Mr. Chairman, the public has already started to use much less aspirin. It is amazing to me the power of television in this regard, and it is going to take some time, labeling or not, for the public to get over the scare that they have had as regards aspirin and a disease about which they know nothing. I doubt even if aspirin was labeled there would be a tremendous change in the use of aspirin. I think the public will eventually forget about this association, since it is not—since it has not been continuing on television, and whether there is a label or not they will continue to use some aspirin in children that have a febrile illness, much like you described your mother did.

Mr. SCHEUER. So I take it you do not consider that the labeling will have much effect one way or the other.

Dr. JOHNSON. No. I think people are so used to using aspirin and acetoaminophen, and by the way they are using more of the acetoaminophen. This is a real hazard for us as regards acute poisoning in childhood, and has been a commonplace occurrence. We try to caution against use of acetoaminophen, yet many families have large, economy-size bottles and poison children as a result. They will continue to use aspirin, labeled or not, much as they continue to smoke no matter what the label is on the package of cigarettes.

Mr. SCHEUER. If you do not think the labeling requirement will have much effect, you might conclude that we are overreacting by holding this hearing.

Dr. JOHNSON. On the basis of my own experience as a pediatrician and from what my partner said before I left on the airplane yesterday, tell them there is nothing to this business of aspirin and Reye's syndrome. We have not seen it. We are having a multiplicity of calls from frightened parents. This makes no sense. And again, it is an unscientific statement, but I have yet to talk to one of my conferees in pediatrics that does not agree.

Mr. SCHEUER. Agree that what?

Dr. JOHNSON. Agree that there is an extremely tenuous if any association between aspirin and the development of Reye's syndrome. The association that Dr. Partin noted, Dr. Eichenwald, and others is the association between influenza B and Reye's syndrome, and perhaps some drugs somewhere sometime play a role in that cascade of events, but the evidence of that is extremely murky and questionable at the present time, and I would include aspirin in that statement.

Mr. SCHEUER. What is the impact on Reye's syndrome of early recognition?

Dr. JOHNSON. That is the key to lowering the morbidity and mortality in Reye's syndrome. It is not, in my humble opinion, preventing children from getting aspirin. It is early diagnosis, and that is where we have a long ways to go, because many practitioners have not seen Reye's syndrome in their training or in their experience. We need much more reasonable publicity about the early diagnosis, because often the parents have the first idea that their child might have Reye's syndrome, and we have to pay attention to that. The

CDC has been very helpful in establishing guidelines for early diagnosis, but the disease has not gotten nearly the publicity it might have, because in the past it really has been the mysterious killer of children. The mortality in the past 8 years has been lowered to about 20 percent in tertiary-care centers, but that is still too high for many of us, of course.

Mr. SCHEUER. To what do you ascribe that reduction?

Dr. JOHNSON. Better treatment in tertiary-care centers, which is extremely important in this disease.

Mr. SCHEUER. Would you make the point that our educational effort to the extent that we make it directed at parents should be to emphasize then the importance of early discovery and to emphasize to parents of kids with flu or chickenpox the importance of looking for the early warning signals of Reye's syndrome?

Dr. JOHNSON. Exactly, Mr. Chairman.

Mr. SCHEUER. I do not want to put words in your mouth.

Dr. JOHNSON. That is exactly right, Mr. Chairman. I would 100 percent agree with that.

Mr. SCHEUER. Is this true whether or not the child is on aspirin—

Dr. JOHNSON. Tylenol—

Mr. SCHEUER. Or no medication at all?

Dr. JOHNSON. Or Compazine, that certainly is true. That is why I tried to point out a few of the features of that very first case, because that still is how children present with Reye's syndrome. That is typical of the last case of Reye's syndrome for instance I saw in Fargo, N. Dak. The first case I saw in North Carolina has great similarity to the cases that are currently occurring.

Mr. SCHEUER. So you think in view of that it is not constructive to single out one medication?

Dr. JOHNSON. No, and I really am concerned about the fact that this current clamor, if I can use that term, is diverting us from the needs of Reye's syndrome in the future. There are a lot of needs, considering the incidence of this disease, the severity of this disease. Funds have been very limited. The National Reye's Syndrome Foundation—I am on the scientific advisory board—is rather delighted about the controversy between aspirin and Reye's syndrome, because that has provided publicity we could not have gotten any other way. Maybe that is wrong, but it has helped us in that way.

Mr. SCHEUER. What do you tell mothers whose kids have flu or chicken pox?

Dr. JOHNSON. Your child is not going to get Reye's syndrome. You watch for the early signs and symptoms of this disease, and I tell them what the early signs and symptoms are, but your child is not going to get Reye's syndrome. If you have anything like persistent vomiting, let me know. I think you have to be blunt in calming them, particularly in light of this current problem that we have all heard about. The discussion on television to a family is a very powerful inciter of fear, much like it was with whooping cough recently. Many parents have come to me and told me for the first time in my years as a practitioner they no longer want to use pertussis vaccine. This vaccine is extremely valuable, yet they have heard

the commentary by NBC on pertussis vaccine which the academy feels is invalid.

Mr. SCHEUER. Dr. Johnson, do you have some concern that if there is a massive educational campaign initiated by the Department of Health and Human Services, as they have proposed, if there are labeling changes on aspirin-containing substances as has been proposed, that the efforts toward early recognition might be impaired by the fact that parents would now believe that Reye's syndrome is a preventable disease, that stopping aspirin administration would prevent any possibility of their kid getting the disease?

Dr. JOHNSON. I tried to allude to that in the presentation. I think this would be the wrong emphasis. If a massive campaign about Reye's syndrome is to be conducted, it should be about early diagnosis and early adequate treatment in the type of center that can manage Reye's syndrome.

Mr. SCHEUER. Do you have the concern that this kind of effort as proposed by the Government could in fact conceivably lead to increased mortality and morbidity because parents would be less alert to these warning signs, which as you have pointed out have a significant chance of reducing morbidity and mortality in diagnosed children?

Dr. JOHNSON. I do not know if I could make that sort of prediction. It is very hard to predict how the public will respond to this type of campaign. I certainly think that is plausible or possible.

Mr. SCHEUER. Dr. Johnson, thank you very much for your forthcoming and very helpful testimony. We appreciate it.

Dr. JOHNSON. Thank you.

Mr. SCHEUER. Next we will hear from Dr. Heinz Eichenwald, professor and chairman emeritus of the University of Texas Health Services Center. Dr. Eichenwald has received more awards, honors, distinctions than we have time to enumerate. He will tell you some of the things that he has done, but I can tell you that he is one of the world's great pediatricians.

We are delighted to have you with us today, Doctor. Please take such time as you may need to cover the high points of your testimony. We have read it. It is exceptionally helpful. So why do you not chat with us informally and cover your testimony as well as anything else that comes to mind, anything you may have heard this morning that elicits your interest.

STATEMENT OF HEINZ EICHENWALD, PROFESSOR AND CHAIRMAN EMERITUS, UNIVERSITY OF TEXAS HEALTH CENTER, DALLAS, TEX.

Dr. EICHENWALD. I wish my mother had heard your remarks. She still is a little concerned that I have not hung out a shingle in the community, but spent my life in teaching and research and in hospital care of children.

Dr. Johnson has already gone over many of the peculiar features of this very curious disease whose etiology we really do not know. As he mentioned, it follows in the United States a number of other common viral infections, but why some children are susceptible while others do not get this illness remains unknown. We do not

understand the mechanism by which these diseases and such toxin as the aflatoxin he mentioned produce the illness, and why some children are susceptible and others not.

Some children in the United States who develop Reye's syndrome have been demonstrated to have aflatoxin in their bloodstream also, but there are other features of the epidemiology of the disease which are striking and which cannot be explained if one invokes aspirin as a cause of this illness.

For example, if you look at cases of Reye's syndrome that are in the very young child, in children under 8 months of age, most of these cases occur among the black and among the Hispanics in the inner cities, but in older patients most cases occur in the white middle-class children living in urban or rural surroundings. So we have this rather peculiar feature, which incidentally for reasons I do not quite understand resembles what poliomyelitis used to be like when it was still a problem disease.

Another important point which bears directly on the studies that have been done recently on Reye's syndrome is the fact that there is no specific diagnostic test for this illness, at least no easily achievable diagnostic test. Diagnosis is based almost entirely on a series of probabilities, and the diagnosis can be made with accuracy only in individuals who are well versed in this disease who have particular experience in dealing with very sick children. I might add that at Children's Medical Center of Dallas, where I work, about 25 percent of the children who are sent to us from other hospitals for the diagnosis of Reye's syndrome turn out not to have it. They have some other illness, but they do not have Reye's syndrome.

The best test we know of to discriminate Reye's syndrome from the other conditions which resemble it and which are due to other etiology is to do a liver biopsy, which is of course an invasive test and one that might produce additional discomfort in this child, and thus people tend to shy away from doing it, but it is the only reasonably accurate way of making this diagnosis.

When the aspirin studies were first published, and particularly the one on which most of the recent disagreement has focused, it became rather obvious to me that there were some features of the illnesses that were being described that differed considerably from what had been going on before.

For example, in the Ohio study the rates of Reye's syndrome were anywhere from 8 to 12 times higher than they should have been in a population of that size. In other words, there was a large excess of cases.

Second, the mortality rates were exceedingly low, as Dr. Johnson has mentioned; even under the best of circumstances one really does not do much better than 20 percent mortality rate. The mortality rates in these studies were 5 percent or less.

And third, the percentage of minor cases, cases that were less sick, stage 0 and stage 1, was considerably higher than that that had been reported in other studies, studies that were most interested in the clinical aspects of the disease, not in the epidemiology. Here were studies which purported to show the effect of a particular substance on the disease where the pattern of the illness ascribed by the investigators, the frequency of the disease, did not

follow what all of us had learned were the major features of the illness.

And finally, fewer than 20 percent of the patients in these studies indeed had a liver biopsy done. Eighty percent did not. Thus, the confidence in the diagnosis I think had to be lowered.

The question naturally came up, How were these cases identified as Reye's syndrome if they did not follow the typical clinical pattern, and if liver biopsies were done only in a small percentage? Well, because of that, I became more interested in these studies, and I have recently had the opportunity to look at the raw data, the case report forms that were submitted by the Ohio Department of Health. A review of these data indicates to me that a percentage of the patients which have been counted as Reyes could not be considered that on the basis of the information that was on these charts.

For example, the investigators overlooked the fact that one of the tests that they relied upon, which is a blood test, that these same increases could occur in children who had mild to moderate viral infections but not Reye's syndrome. For example these increases are very common in chicken pox, influenza, flu gastroenteritis—a disease associated with vomiting. If you rely on that alone, you are going to overdiagnose the illness.

Second, a number of the patients who were called Reyes did not have one of the other chemical tests which are found elevated in patients with Reyes, the serum ammonia level. These patients had normal levels, levels which should have caused the investigators to wonder whether they were indeed dealing with Reyes or not. So there was considerable doubt about some of these patients that were included in this study as Reye's syndrome. The patterns, the diagnoses were simply not correct or could not be looked upon with a great deal of assurance. And this concerned me, and I became actively involved in all of this business, and this is why I am here today.

I might also mention that when the raw data finally became available, a pharmaceutical company asked six well-known pediatricians in the United States and in the academic community to review the data for them and to recommend to them what this group felt appropriate action should be. This group consisted of people who are a well-known group: Dr. Sidney Gellis [phonetic] who was until recently chairman of the department of pediatrics at Tufts; Dr. Robert Heckelman [phonetic], Phillip Manskoski [phonetic], a professor in the Downstate Medical Center in the State of New York, Dr. Henry Madler [phonetic], who is presently dean of the medical school at Wayne State in Detroit and was formerly professor and chairman of the department of pediatrics at Northwestern University, Dr. Irving Shulman [phonetic], chairman of pediatrics at Stanford University.

Just to indicate to you the intellectual level of these people, I counted that between the six of us we had written 17 books and authored nearly 1,000 articles in the pediatric literature, and served on every editorial board in the United States, and also in some cases in Europe where pediatricians were represented. So these individuals I believe are able to offer at least reasonably good judgment.

At the conclusion of their review of the data that were available, the raw data, not just the data that was published, the following telegram was sent to the Secretary of the Department of Health and Human Services:

We know that agencies of government charged with protecting the public's health have made serious efforts to examine objectively the controversy surrounding aspirin and Reye's syndrome. At the suggestion of Glenbrook Laboratories we met to review the major statements made, as well as to learn of a new analysis made of the Ohio study, the one that the FDA considers the most worthy of extensive analysis. Numerous flaws have been cited by scientists in the four major studies associating Reye's disease with aspirin. We concur with the findings, but the methodology was flawed. We are disturbed to learn that the raw data was never analyzed by independent agencies until recently. This lack of analysis of raw data was a serious gap in the scientific process. We have seen a preliminary review of the raw data of the second Ohio study as analyzed by the Biometric Research Institute. Some of the major conclusions reached by this group are there was a significant question whether all cases reported as having taken aspirin had actually taken that medication. Nothing in the data confirmed whether medication bottles were actually seen by interviewers.

Additionally in four cases the presence of aspirin in the medication was assumed, but could not be determined from the data.

If two cases used the nonaspirin medication, only two cases were wrong and the study would fail to show a significant association between rise in normal aspirin use.

In other words, we are talking about very, very small numbers.

It affects some parents of Reye's victims. In the second year we have been citing brands of drugs that have not contained aspirin at all. Based on our review and discussion, we urge the Secretary and the distinguished objective scientists to review this new data.

The panel should consist of prominent scientists who have not expressed opinions in the past concerning the association between Reye's and aspirin and thus whose objectivity cannot be questioned by either proponents or opponents of the Reye's/aspirin association.

Any labeling should be delayed until such a review is completed. Labeling aspirin to warn against its use in influenza and chickenpox may be a premature activity. It may have public health consequences far more serious than the intent it has to cure.

In the past more pediatricians—between fever caused by influenza or nonspecific upper respiratory infection—in other words, warning against aspirin use in influenza is a warning against it in the fibril child.

Aspirin has been used safely and effectively by hundreds of millions of children over the last 80 years. It is a drug which has been widely studied and its widespread use represents one of the largest clinical trials ever made.

We are certain that the Government would not wish to tamper with so important and universally accepted a medication without substantial and compelling cause.

Clearly no one in Government, private practice, or the scientific community wants to see any beneficial drug disappear from use.

The safety of children is the single most important responsibility for all of us and we are convinced the Government is trying to act diligently in exercising that responsibility. However, short-term solutions should not set the stage for removal of a time honored and useful drug.

A precipitous warning on aspirin labels may do just that.

That is the end of the telegram by the six pediatric professors whose names I mentioned before.

I would make two final points:

First, I reviewed recently the so-called CDC criteria which were used by the investigators of the first and second Ohio study and also by the Michigan study. I compared them to cases that I knew, on the basis of liver biopsies, had Reye's syndrome. Relying on these two criteria for the diagnosis according to the information I now have will give you a 20-percent range of recovery.

In other words, you will overdiagnose approximately 20 percent of the cases. Since this was the only criterion used by these investigators, one would have to conclude on the same basis that 20 percent of their cases were not Reye's syndrome.

If you get into that situation, any type of statistical analysis that you apply to the data is meaningless. What you have is what is now known as a garbage in/garbage out situation.

I have been informed recently that another very prominent investigator has also compared the CDC criteria to his own clinical material and has arrived at the conclusion that at least 25 percent of patients will be misdiagnosed by the application of these criteria.

Now the final point.

Most people I believe consider aspirin to be primarily an anti-fever drug and an antipain drug which of course it is, but it has one inherent property which is serious physically in pediatrics and that is its anti-inflammatory effect.

Many children with diseases such as rheumatoid arthritis and rheumatic fever are on aspirin for very long periods of time. These drugs are capable of reversing to a large degree the effects of these two crippling diseases.

What has happened since the media publicized the apparent relationship between aspirin and Reye's syndrome has been, as Dr. Klein, I think, will also testify, many calls to us from patients who are very disturbed that their children with these rheumatic diseases are on aspirin and many of these parents have asked a physician or demanded of the physician that these medications be stopped.

The point is that all other available medications, other medications that would have the same effect of aspirin, be far more toxic in children, are also far more expensive. What is already happening is that children who should be receiving aspirin and who would be receiving it perfectly safely are now on expensive drugs that produce major side effects because the parents feel that is a safer approach than giving aspirin.

So the publicity has already done much damage and I believe if the label ever appears or if the Department launches a major campaign to convince parents not to use aspirin, then I think the remaining parents who have those children who have to be on this agent will cause this drug to be withdrawn and expose the child to far graver consequences than any risk they have at present.

[The prepared statement of Dr. Eichenwald follows:]

STATEMENT OF HEINZ F. EICHENWALD, M.D., WILLIAM BUCHANAN PROFESSOR OF
PEDIATRICS, THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS

I have taught, practiced, and conducted research in the field of pediatrics for the past 30 years. I also received training and worked in epidemiology at the Centers for Disease Control and while there directed an epidemiologic study of the effect of gamma globulin injections on the incidence of poliomyelitis and subsequently served as the head of the unit investigating the epidemiology of hepatitis in the United States. My major research interests for the past 25 years have dealt with infectious diseases, especially those capable of damaging the central nervous system of infants and children. These activities have led me to study other aspects of brain injury, work that was recognized by the award of the Humboldt Prize for Research by the West German Republic in 1979 and the Weinstein-Goldenson Award for Medical Research of the United Cerebral Palsy Foundations in 1980. I mention these events only to show that I have had a continuing interest in various aspects of central nervous system damage and in liver disease, the two organs most involved in Reye's Syndrome. I am obviously greatly concerned about any factors that might lead to brain damage since most of my life has been spent in activities to prevent such untoward effects.

As you know, we do not know the causes of Reye's Syndrome. First described as a distinct clinical entity by Dr. Reye in 1963, it is likely that the illness occurred prior to that time but was given other names. I remember a few children that I saw prior to 1963 which, in retrospect, almost certainly had Reye's Syndrome but I called them something else. In any event, as the term "syndrome" implies, the illness almost certainly has a number of different causes. I saw cases clinically indistinguishable from Reye's among Vietnamese children in the Delta area of South Vietnam and among Thai children in their country. These cases were clearly due to the ingestion of

a toxin produced by a common fungus that grows on rice and other cereals. This exceedingly poisonous product is called "aflatoxin"; it is perhaps of more than passing interest that one investigator demonstrated this same substance in the blood of a number of American children who developed Reye's Syndrome.

What are the other possible causes of this curious disease? We know that it can follow chickenpox, as well as many other common viral infections such as influenza, especially type B, but only a very small percentage of children infected with these viruses develop Reye's Syndrome. What the mechanism is whereby these infections or the aflatoxin produce the illness is not known, the best theory is that they damage a structure in the cell called the mitochondria whose function is essential to normal cellular metabolism. Why some children are susceptible while others are not also remains unknown. Many aspects of the epidemiology of the disease cannot be explained, especially if aspirin is postulated to be a cause. For example, cases among children less than eight or so months of age tend to be found most commonly among the black and hispanic poor in the central cities while older children developing the disease tend to come from the white middle-class, living in suburbs or rural areas. No explanations for this pattern of occurrence have been advanced.

Another important fact is that there is no specific diagnostic test for Reye's Syndrome. In other words, the diagnosis is based on a series of probabilities and thus there often is considerable room for error. This is demonstrated by the fact that about 25% or more of children sent to the Children's Medical Center of Dallas, where I work, with the diagnosis of Reye's made at another hospital turn out to have a different illness. There

are a number of conditions, metabolic, infectious, or toxic in origin which resemble the syndrome closely and which often can be clearly differentiated from Reye's only by studies not generally available in community hospitals. A liver biopsy is very often required to confirm the diagnosis, an invasive and often painful procedure, which many physicians may not wish to perform. Nevertheless, there is a notable lack of biopsies to confirm cases reported in the studies that purport to show a link between aspirin and Reye's; the rates are far lower than in other reported series.

Reye's Syndrome may vary in severity from an illness easily overlooked or thought to represent gastroenteritis or simply a stomach upset, to a condition which rapidly progresses to death within two to three days after onset. In recent years, our ability to treat the changes that the disease produces in the body has improved considerably but usually around 20% of children still die. In the studies that attempted to link aspirin to the disease, mortality rates were much lower, again suggesting the possibility of incorrect diagnosis.

To summarize what I have said up to this point: 1) Reye's Syndrome is a rare condition affecting children. 2) The syndrome is associated with a number of different causes such as aflatoxin but in the United States seems most frequently to follow a number of common viral infections. 3) We do not know what renders certain children susceptible nor do we know why others seem resistant. 4) We cannot explain the peculiar epidemiology of the disease. 5) No specific diagnostic test short of liver biopsy exists and thus many children are diagnosed as Reye's Syndrome who do not have it or conversely, patients who indeed have the disease are misdiagnosed. 6) A number of metabolic, drug induced, infectious, and hereditary disorders are

known which mimic the signs and symptoms of Reye's Syndrome and are difficult to distinguish from it.

The information I have just presented bears directly on the issue of the effect of the administration of aspirin on the development of Reye's Syndrome. Obviously, a fundamental basis for any study is the correct identification of cases. If even a small percentage of patients is misdiagnosed, the results of studies that tend to incriminate one factor or another become so flawed as to be uninterpretable. The biostatisticians will illustrate for you the special problems of so called "case-control studies" on which the whole thesis that aspirin plays some role is based, and how the available information cannot be interpreted as showing that aspirin is at fault. What I would like to point out to you is another important flaw: the correct identification of cases. Few liver biopsies were done and the diagnosis in these studies was based primarily on what are called the "CDC Criteria". I can assure you on the basis of my own experience that application of these criteria, even when done correctly, and even assuming that there are no errors in the laboratory results obtained, still result in a incorrect diagnosis in at least 20% of cases, especially the milder ones, which represented the great majority of the cases in the "aspirin studies".

Furthermore, my own examination of the data on which the published studies are based, carried out independently from the biostatisticians, has led me to the same conclusion: the studies cited in support of an association of aspirin administration and the development of Reye's Syndrome are so flawed and contain so many biases that they cannot be interpreted as showing an aspirin effect. It is worth pointing out that individuals, committees or organizations that have arrived at conclusions different from

mine had not reviewed the individual case reports and/or the raw data.

One might well ask "what is all the fuss about, shouldn't we just play it safe and tell parents not to use aspirin if their child has a flu-like illness or chickenpox?" Almost any respiratory or gastro-intestinal infection in a child can be "flu-like", but more important is the fact that in children aspirin has uses other than the control of fever. The most important ones deal with the ability of this drug to diminish inflammation from a variety of causes and to do this more safely than other available agents. For example, aspirin is usually prescribed for children with several diseases of connective tissue such as rheumatic fever and rheumatoid arthritis. No other agent is as safe and/or effective as aspirin for the control of the manifestations of these illnesses in children. What has recently happened, because of the information published by the media about the supposed association of aspirin and Reye's Syndrome is that many parents have asked, and in some cases demanded, that their physician discontinue the use of the drug in their child and prescribe some other agents. This has not only been the experience in our own institution, I have had telephone calls from rheumatic disease specialists in the other parts of the United States asking what they should do. They realize, as I do, that there are no other agents that are as safe, effective and inexpensive as aspirin in the treatment of these crippling illnesses.

I believe that placing a warning label on aspirin, as the Secretary of the Department of Health and Human Services has proposed, is not based on scientific evidence or on a correct analysis of available data and does not serve the welfare of children. His decision will cause many children who need the aspirin for its anti-inflammatory and pain-relieving properties to stop receiving it and other drugs will be substituted which are inherently much more toxic than the drug they are replacing.

Mr. SCHEUER. Can you tell us what the annual patient population is that has Reye's syndrome?

Dr. EICHENWALD. Almost certainly less than 1,000 cases per year; probably in the range of 600.

Mr. SCHEUER. What would the normal patient load be annually for rheumatoid arthritis and rheumatic fever?

Dr. EICHENWALD. Rheumatoid arthritis, probably 5 to 10 times that. I really can't say.

I believe Dr. Klein can give you better figures, but they reported some 1,100 cases of rheumatic fever last year in the United States.

Mr. SCHEUER. We have been informed that at any one time there are approximately 150,000 children suffering some kind of fibril, juvenile arthritis for whom aspirin is by far the best treatment modality.

Dr. EICHENWALD. Yes, sir, it is the safest and least expensive.

Mr. SCHEUER. So as I get it—and I am trying to sum up the education I have received here this morning which has been extraordinarily interesting—the main game, as far as the parents of kids who are suffering rheumatoid arthritis and rheumatic fever, is aspirin, and as far as parents of children with chickenpox or the flu, the main mission it seems to me of Government and the private medical community is to emphasize to them to be on the lookout for early warning signals of Reye's syndrome, that that is the important mission there.

Dr. EICHENWALD. That is correct.

Mr. SCHEUER. It seems to me if Government has a limited capability of intervening, that they have sort of missed the boat in putting their effort and resources into labeling rather than into some kind of education message to parents to be alert for early warning symptoms of Reye's syndrome.

Dr. EICHENWALD. Yes, sir.

Mr. SCHEUER. They intervene at the wrong point.

Dr. EICHENWALD. And intervene on the basis of totally inadequate scientific data.

Mr. SCHEUER. Let's talk about that scientific data.

In your opinion, is it possible for the medical profession or for the government to make accurate judgments about the relationship of Reye's syndrome to aspirin without having evaluated the case studies and the raw data?

Dr. EICHENWALD. It is impossible to make that decision without the raw data, sir.

Mr. SCHEUER. So you are saying then, Dr. Eichenwald, you would say that just on those grounds alone that the second Ohio study is flawed, perhaps fatally?

Dr. EICHENWALD. Certainly my view of the raw data which the various agencies in and out of Government who made recommendations about Reye's syndrome have not seen. By having seen this data at my request, I am convinced from the data that no one would have arrived at the conclusion that there was an association with aspirin and Reyes.

Mr. SCHEUER. Do you have any information as to whether the top experts from whom the Secretary of Health and Human Services, Secretary Schweiker, draws his counsel and advice, whether those

top experts had evaluated the case studies and the raw data prior to advising the Secretary?

Dr. EICHENWALD. I know that prior to the publication of—from the Center for Disease Control concerning this problem, the Center for Disease Control had not seen the raw data. In fact the raw data was only forthcoming after one of the pharmaceutical companies filed a Freedom of Information Act suit and it was only through legal action that these raw data were made available.

At the time this happened, recommendations had already been made by other official and unofficial bodies such as the American Academy of Pediatrics about the relationship, but they had not seen the data.

I am convinced if they had seen the data they would have arrived at the same conclusion that these six prominent pediatrics professors did who had seen it at that time.

Mr. SCHEUER. And the CDC experts at the time they advised the Secretary had also not seen the raw data and the case studies?

Dr. EICHENWALD. To the best of my knowledge, that is correct.

Mr. SCHEUER. Our subcommittee counsel would like to ask a question.

Mr. SHACKNAI. Based on your experience and your many years of experience in practice and academic pediatrics, is it your feeling that the peer review seeks to bring into review dispassionate individuals who have not previously expressed an opinion on the studies being considered on the matter at hand?

Dr. EICHENWALD. Yes, that is the way things are usually done.

Mr. SHACKNAI. Are you aware, sir, that in a May 24, 1982, workshop convened by the Food and Drug Administration and the CDC jointly, there were 16 participants and that 7 of those 16 participants had previously participated in October 1981 in a panel which reviewed the same data and an additional participant, Dr. Starko, had been a principal investigator in one of the studies being considered at the May 24th workshop?

Dr. EICHENWALD. I did not have that information, sir.

Mr. SHACKNAI. Given that information as you have been presented with it, would you conclude such a group would be able to proceed in a way and render a dispassionate view that is not in any way prejudiced by prior information, right or wrong?

Dr. EICHENWALD. No, it would be an inappropriate group, particularly since this group proceeded without knowledge of the raw data.

Mr. SHACKNAI. Are you aware also that that group was not able to reach consensus, given whatever predispositions they may have had by virtue of prior disclosure to summaries of the studies?

Dr. EICHENWALD. I would not know that, sir.

Mr. SCHEUER. Dr. Eichenwald, I have known Secretary Schweiker since he was a member of the House and I have the utmost respect for his total integrity, for his caring about kids, the entire American public.

He is an extraordinarily fine human being.

I have also had a great deal to do with CDC. I have absolutely no question about the decency and the bona fideness of the top experts at CDC.

Yet perhaps your phrase, garbage in/garbage out best characterizes your feelings about the scientific data base on which they took this important step of mandating labeling.

How do you explain what they have done? These are all decent, well-motivated men. How could this system have fallen apart? How could it have gone so awry?

Dr. EICHENWALD. That is very difficult to say. I think as the counsel mentioned, these decisions can only be made on the basis of the best available information. I think the decision was made not on the basis of the best available information.

I believe confidence was placed in some computer printout and tables that had been constructed by individuals who patently were unable to diagnose Reye's syndrome with a great degree of accuracy.

Also, as I indicated, I think the published information was not scrutinized in a way that it should have been; namely, why are there so many cases in Ohio? Why are there so many mild cases? Why did so few children die of this disease? Why were so few liver biopsies done? Why are we told so little about the critical course of these patients? I think to ask those questions takes a good deal of experience in clinical pediatrics.

The CDC is not a clinical organization. I don't believe Secretary Schweiker has gone to medical school. I think it was the fact that the polished data was accepted without question; that is, people make mistakes.

I think the mistake was made in this particular case.

I certainly would not wish to infer that the Secretary or the CDC took their stands because they were being malicious. I think they did it with the best of intentions, as we pointed out in the telegram.

But I believe they were misinformed about the information that was available.

Mr. SCHEUER. Counsel has a question.

Mr. SHACKNAI. As you are aware, Dr. Eichenwald, since your telegram and otherwise, there has been a great deal of public discussion and controversy on this. Certainly the view of such distinguished individuals as yourself and others have been known to the Secretary and others in positions of responsibility at HHS.

Do you have any theory or personal view as to why they seemingly disregarded this information and planned to proceed with the labeling and public education effort you have personally called destructive?

Dr. EICHENWALD. I do not understand why, and I could not even offer a reason why they should be.

Mr. SCHEUER. The witness just prior to you, Dr. Johnson, indicated that he didn't think the labeling requirement would have any significant results pro or con.

You apparently feel that the requirement for labeling will have very deleterious results. Would you elaborate on why?

Dr. EICHENWALD. I not only feel so, I know so, because since the media reported this apparent relationship I have had telephone calls from rheumatologists, the individuals who take care of children with rheumatic diseases, from five medical schools asking me

what they should do because of the flood of calls they are receiving from parents who want to have their kids taken off aspirin.

Our own rheumatologist, Dr. Chester Fink, who has a large clinic of patients with rheumatoid arthritis, probably around 600 or so, has been under the same pressure.

In other words, parents want their kids off aspirin irrespective of the risks to that particular child, irrespective of the warnings that the other drugs that could be given instead of aspirin are considerably more toxic.

From that alone, one has to conclude that a deleterious effect has already occurred and if the label appears I think it will be the end of the use of aspirin in children for any reason at all.

Mr. SCHEUER. That is a very strong statement.

Dr. EICHENWALD. It is based on a lot of experience. The parents do not want to take chances with their children. They may smoke when it says on the cigarette package that the Surgeon General has found, et cetera, but they will not give their children medications with a warning label on it, and pediatricians would be very reluctant to recommend this because of the possibility of a malpractice suit if something should happen.

In other words, one—

Mr. SCHEUER. Dr. Johnson is nodding his head vigorously on that statement.

Dr. JOHNSON. Yes, I agree, vigorously agree.

Dr. EICHENWALD. It would be very difficult.

Dr. JOHNSON. That is why all my partners clamored to have me come because they are fearful of this and rightfully so.

Mr. SCHEUER. Thank you.

Dr. EICHENWALD. I personally feel aspirin is the best antipyretic, antifever medication that we have and even that is a very important use which will disappear completely.

Mr. SCHEUER. And you fear that literally thousand of kids who are suffering from fibril diseases, rheumatoid arthritis, who should be getting aspirin, will not be getting aspirin because of their parents' misplaced apprehension that aspirin will be harmful to them in treatment of the disease that they have which is not Reye's syndrome, but which is rheumatoid arthritis for which aspirin is absolutely the right medication?

Dr. EICHENWALD. Yes, sir.

Mr. SCHEUER. Doctor Eichenwald, you have given us superb testimony. very impressive. We are grateful to you for your time and effort. Thank you very, very much.

Dr. EICHENWALD. Thank you, sir.

Mr. SCHEUER. Next we are going to hear from Dr. Robert Klein, director of the Dartmouth-Hitchcock Arthritis Center on their program of juvenile arthritis.

Dr. Klein, we appreciate your coming here this morning. We have received your testimony. We will be very happy to have you give us the highlights of your testimony and refer to anything else that comes to mind.

If any of the testimony or exchanges we have had this morning with the two preceding witnesses peak your interest, stimulate any thoughts on your part, please comment as you wish.

Please proceed.

STATEMENT OF ROBERT KLEIN, M.D., DIRECTOR, DARTMOUTH-
HITCHCOCK ARTHRITIS CENTER, HANOVER, N.H.

Dr. KLEIN. Thank you very much, Mr. Chairman.

A lot of the things that I was going to say have already been alluded to so I will summarize.

Since people first began using willow bark back in the middle of the 1700's, which contained aspirin—

Mr. SCHEUER. Willow bark?

Dr. KLEIN. Bark from the willow tree, yes. Since then people have been using aspirin for many occasions.

Mr. SCHEUER. Willow bark contains the essential ingredient for aspirin?

Dr. KLEIN. Salicylate, that is right.

And since the late 1800's people have been using aspirin for the treatment of rheumatoid conditions.

This is therefore a very important thing for any physician who has been taking care of children because aspirin is the mainstay of our practice for children with rheumatoid arthritis.

There are probably 150,000 children in this country, figures range from 250 to 260,000.

From my looking at it, that seems to be a fairly appropriate number.

Mr. SCHEUER. At any one time?

Dr. KLEIN. At any one time in the United States alone.

Mr. SCHEUER. How many would that be in the course of a year?

How many new cases per annum?

Dr. KLEIN. Oh, per population of children it would probably be about 1.5 to 3 the estimates go, per 10,000 children.

Mr. SCHEUER. How many would that be in the United States? Can you translate that for us?

Dr. KLEIN. New cases per year?

Mr. SCHEUER. New cases per year in the United States.

Dr. KLEIN. I would have to stop and think about the population numbers but the incidence, the figures would show in many thousands of new cases per year.

So we are talking about in a small State such as New Hampshire alone where I come from in practice, where the population would be several hundred thousands, we are talking about several hundred new cases per year.

Of course, that would be magnified largely as we get to the populations in the different States.

Mr. SCHEUER. Tens of thousands then.

Dr. KLEIN. Oh, yes.

So with this number of patients, people caring for these children became very worried about the possible association. The association worries us because the incidence occurs at a peak age of 1 to 3 years of age, and therefore these children are starting on their aspirin therapy before they begin the viral illnesses, chicken pox, influenza and other diseases associated with Reye's syndrome.

We use a lot of aspirin, we use it in a dosage of 75 at the 100 milligrams per kilogram per day. That comes to a blood level of 20 to 30 milligrams percent. So these children are having high-dose aspirin therapy before they contact any of the illnesses.

So one of the problems in identification of these cases is did they have the aspirin before they came down with Reye's syndrome. Here is a population of children, significant numbers, that are on aspirin therapy day in and day out and during the flu season and during chicken pox and during other things.

It became pretty obvious that this would be a population to look at. So when the first reports started coming out, I contacted the heads of 10 juvenile rheumatoid arthritis clinics and asked for their experience from around the country.

I was surprised and relieved to see that there were a handful of cases particularly in some areas where they are clustered but not as many cases as one would expect to see if aspirin were really of significant importance in the development of Reye's syndrome.

Since that time at the Pan American Rheumatology Meeting here in Washington in June, an associate of mine from the University of Rochester, Dr. John Bauns and I have polled 25 heads of clinics, and several people from South America, England, and other places. We find that there are a handful of cases of Reye's syndrome but not the increased incidence apparently one would expect to see.

For this reason, and because of all the controversy right now, we have developed a protocol—and we hope we are going to get it out to people in a very short period of time—of actually looking into every case of suspected Reye's syndrome to see if it's actually Reye's syndrome or what is going on.

We do know that aspirin can affect liver enzymes, exactly the test that Dr. Eichenwald mentioned. This is not picked up clinically but because we get more sophisticated with laboratory diagnosis we get elevated blood. But we know it is transient and within 3 to 6 months it disappears.

After polling these people around the country we discussed at great length what other medications we could use. I think it should be stated that aspirin is our mainstay therapy because all other medications that have been prescribed for rheumatoid conditions including rheumatic fever and juvenile rheumatoid arthritis and other diseases, vasculitis, things like this, aspirin is the drug against which all other drugs are tested. In other words, we look for efficacy and safety in other drugs by comparing them to aspirin.

We find no other drug that is as safe and certainly we don't know about the possible dangers of many other drugs. They have not been looked at, the nonsteroidal anti-inflammatories, and no drug at the present time that is a firstline drug is as effective as aspirin in rheumatoid arthritis.

This has caused a lot of questions. I spoke to the chairman of the Pediatric Council in Rheumatology just last night and we discussed how many of us are receiving phone calls from patients about the fear of the use of aspirin. It is a very significant number, as you can imagine.

We actually now, when we start something on aspirin as we always do, indicate all the possible side effects but now we find ourselves really having trouble trying to get people to take aspirin.

Mr. SCHEUER. Even though it is by far the best drug available.

Dr. KLEIN. Certainly it is the drug of choice. I don't think you will find a head of a rheumatoid clinic that wouldn't say, that for children.

So I think the information that went out has affected our practices and will go on affecting our practices no matter what happens as far as labeling goes until this is cleared up one way or the other.

We hope to show with this study we are proposing now that aspirin at least would be a safe drug in this section of the population, that is, the section of children with rheumatic conditions.

There are other things that I wish to say but I think that Dr. Eichenwald and Dr. Johnson have already said some of the things, so perhaps I will stop here.

[The prepared statement of Dr. Klein follows:]

TESTIMONY TO THE SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE,
RESEARCH AND ENVIRONMENT

James H. Scheuer, Chairman

There are many indications for the use of aspirin at the present time. I wish to base my statements on the use of aspirin for rheumatoid conditions and, in particular, juvenile rheumatoid arthritis. Data would suggest that there are approximately 150,000 children currently taking aspirin for this indication on a chronic basis, in the United States alone. The dosage of aspirin is approximately 100 mg., per kg., per day, bringing a therapeutic blood level between 20 and 30 mg., per cent. Since the peak incidence of arthritis in these children is one to three years of age, these children are taking aspirin prior to and during the ages when viral illnesses, including influenza and chicken pox would be prevalent. Therefore, the reports about a possible association between aspirin usage and Reye's syndrome are of extreme interest for physicians caring for these children.

I, therefore, began writing to the heads of the juvenile arthritis clinics around the country to see what their experience had been with Reye's syndrome since this seems like an important and likely group to study. In polling a wide range of doctors across the United States, there may be areas where there were a few reported cases of Reye's syndrome, but clearly the majority of physicians caring for children in arthritis clinics had not seen a significant amount of Reye's syndrome. No one has grouped the patients and looked into this in detail and since aspirin, of course, can cause a transient elevation of certain liver enzymes when treatment is begun it is not really clear whether those few suspected cases are really Reye's syndrome. For this reason now, after polling approximately twenty-five doctors across the country, we are developing a protocol which will be ready within the next month. We are hoping to have the cooperation of the heads of all the juvenile arthritis clinics around the country, so that we can look into suspected cases of Reye's syndrome in great detail.

Back in April, 1982 I wrote a memo to the house staff and I enclose it, since little in the situation has changed except I can now say that instead of having polled ten physicians, we have now spoken to twenty-five physicians who head juvenile rheumatoid arthritis clinics. One must be cautious and quite concerned until the question of possible association between aspirin and Reye's syndrome is resolved, but it still seems evident that all of the heads of these clinics would continue to use aspirin as the drug of choice for juvenile rheumatoid arthritis. In fact, all other medications for treatment of this illness are compared to aspirin as a baseling medication for arthritis in children. No other non-steroidal anti-inflammatory medication appears to be better and since their effects on mitochondria and prostaglandins are similar to aspirin, there is no evidence that they would be safer.

Robert B. Klein, M. D.

Robert B. Klein, M. D.

Director, Juvenile Arthritis Clinic
Dartmouth-Hitchcock Medical Center

9-15-82

RBK:ls

HITCHCOCK CLINIC A component of Dartmouth-Hitchcock Medical Center

Hanover, New Hampshire 03755
603/643-4000

April 8, 1982

TO: PEDIATRIC STAFF AND HOUSE STAFF
FROM: ROBERT B. KLEIN, M.D.
RE: ASPIRIN INGESTION AND REYE'S SYNDROME

As you all know by now, the American Academy of Pediatrics has recently assigned a group to study the question of an association between aspirin ingestion and Reye's syndrome. Their findings published late in February indicate that "there is strong epidemiological evidence for an association between the occurrence of Reye's syndrome and the prior taking of medication containing salicylate." They go on to say, "On the other hand, there are methodologic difficulties in each of these studies which warrant caution in interpreting the meaning of this association." In other words, they feel that there is some association but no obvious cause. Unfortunately, the working group has said its consensus was that, until the nature of the association between salicylates and Reye's syndrome is clarified salicylates should be avoided whenever possible for children with varicella infections and during influenza outbreaks. It also cautioned that all antipyretic medications for those illnesses be avoided, except when the need to reduce high temperature outweighs other considerations (clinically, this is obviously difficult to evaluate).

This issue could be addressed on two levels. First of all, the use of salicylates in the treatment of rheumatoid conditions of children, and two, where salicylates would be used for fever control for other acute illnesses.

I would like to take up the issue of rheumatoid conditions of childhood. The problem of aspirin usage in its relationship to Reye's syndrome is an unclarified one and publicity in this area has caused much difficulty. Taking the children off their aspirin would cause them much distress and, in addition, they may well have a relapse of a very serious condition which was being well controlled with aspirin. The publicity and the press on this issue has also caused much distress for the families. I have recently contacted the heads of ten juvenile rheumatoid arthritis clinics around the country from the west coast to the east. After what seems like approximately 150 years of clinical expertise, the heads of these clinics report to me that they have not seen a case of Reye's syndrome that was obvious. Even looking through some of the questionable reports in the literature, at most there are a handful of suspected cases, in spite of the fact that hundreds of thousands of children have been on aspirin at dosages producing a serum level in the therapeutic range between 20 and 30 mg., per cent. During these times these children have gotten viral illnesses, influenza and chicken pox and have not seemed to develop Reye's syndrome.

To conclude, I am puzzled by any association of aspirin with Reye's syndrome. Obviously, I feel that many more studies need to be done and each of the cases needs to be looked at critically. In the meantime, it is regrettable that the amount of publicity has caused distress in the families of children with juvenile rheumatoid arthritis who are trying to interpret the conflicting press releases.

It is also quite obvious that salicylates are extremely important in other rheumatologic problems, other than juvenile rheumatoid arthritis. For example, we see a fair amount of Kawasaki's syndrome since we had that epidemic in the New England area last year and it has clearly been shown that in this illness steroids would be contraindicated.

and aspirin for its anticoagulation effects as well as its anti-inflammatory effects is the drug of choice. Other vasculitis syndromes, as well as rheumatic fever, could also be put into this category. Aspirin is an extremely important drug for the treatment of rheumatological problems in children.

On the basis of my contacts around the country, all of the heads of the clinics feel that aspirin is still the drug of choice in juvenile rheumatoid arthritis, except for perhaps some rare forms where ankylosing spondylitis would be involved. Perhaps there, one of the other non-steroidal anti-inflammatory drugs would be better. None of the heads of the clinics, however, wished to change to any of the other medications because there is no indication that they would be safer and they certainly do not feel that they are as efficacious in children as salicylates. Therefore, on the basis of the scanty evidence and literature it seems unlikely that Reye's syndrome is a major problem in the salicylate treatment of juvenile arthritis and since salicylates are the drug of choice we should continue to use them.

R.B.K.

RBK:ls

Mr. SCHEUER. Well, I thank you for your very excellent testimony. Let me just dwell for a moment on the question of the proliferation of lawsuits that could conceivably result from this, and the fear of malpractice suits. Because if you set an ape down in front of the typewriter, ultimately he would type out all the plays of Shakespeare, and even though there may well not be a cause-and-effect relationship between aspirin and Reye's disease a child, some children, somewhere, at some point in time who are given aspirin for rheumatoid conditions, may ultimately get Reye's disease.

If I were a doctor, if I were a doctor who specialized in rheumatoid illnesses as you do, Dr. Klein, and I knew that the Government had raised the early warning signal on the relationship between aspirin and Reye's disease and I had a child with a rheumatoid condition for whom aspirin is the best drug of choice available to me in my armory, I might worry about this ape in front of the typewriter and I might say if I am the guy who will be hooked when he types out the last one of those plays of Shakespeare I don't want to face a malpractice suit. Am I being paranoid on behalf of the medical profession, or is that a lingering doubt in the back of my mind that physicians might well share?

Dr. KLEIN. I share it completely myself and I don't hear any paranoia. Even at the present time we are very concerned about the use of aspirin, and as you can imagine, the Council on Pediatric Rheumatology has been contacted many, many times for statements. I am contacted for statements frequently and refer people to the foundation.

It is very difficult to come out with a statement. We think in terms of rheumatoid conditions as just affecting the joints, but there are forms of juvenile rheumatoid arthritis that affect the heart, inflammation around the lining of the heart.

We can get internal organ abnormalities and other things. We are faced with a situation where in the winter a child has a fever. Could be getting the flu, any other viruses, or it could be a relapse of their arthritis and it could be the affecting of an internal organ or some other situation.

We are really in a very difficult situation at that point because if we stop the aspirin, and medically-legally that is probably what most people would do, we could see some serious effects of that on the child's therapy, effects that could be deleterious.

Mr. SCHEUER. To put it clearly, there would be a retardation in the child's physical condition.

Dr. KLEIN. Absolutely, that is possible. So I think people are concerned in dealing with arthritis, physicians are concerned, we are confronted by patients who are very concerned, and rightfully so, from the amount of controversy, and of course some final word on this would be excellent.

Again, this is mainly what prompted us to start this study because we at least wanted to prove in one subset of people whether there seems to be an association so we can come up with a statement that is appropriate at least for that group of patients.

Mr. SCHEUER. Our minority counsel, the very distinguished and hard working and competent minority, Ms. Bach, has a question.

Ms. BACH. Thank you, Mr. Chairman.

Dr. Klein, given the fact that it has been stated that the damage has already been done, that is the decision of HHS to come out with this warning, should HHS change their position (if there is some possibility that they would come back and detract what they have said) or would go back and look at the data and subsequently change their status, in your opinion what would be the most appropriate way in which they should present that?

Second, how would the patients and physicians accept or not accept and have confidence in a HHS change in position, and what effect would that have on aspirin use?

Dr. KLEIN. Those are excellent and very difficult questions on which I must somewhat speculate. But if the HHS finds that the data do not justify a review by a panel as Dr. Eichenwald suggested, or by independent analysis, then it seems clear that an indication that was specific to the physicians of the country and to the patients of the country would be very helpful. I think as it stands right now, rheumatologists feel it's the best drug and is the drug of choice, but we feel very restricted and in a very difficult posture in using the medication and explaining it to the patients.

Ms. BACH. Would you regain the confidence of the patients?

Dr. KLEIN. I think it would help. If we are saying that in spite of a warning and in spite of a lot of controversy we persist to use a medication, it would certainly give us a certain amount of indication. We are talking now about the indication to use it for rheumatoid conditions. I want to make that clear. I am not talking here specifically to the idea of using it as an antipyretic or other forms which I don't consider myself to be an expert on.

Ms. BACH. Thank you.

Mr. SCHEUER. Our distinguished, very hard-working counsel, Mr. Shanknai.

Mr. SHANKNAI. If I could follow up on that question, Dr. Klein. I am not sure your answer was entirely responsive to it.

I think what Ms. Bach was trying to elicit was a response as to whether or not if, after undertaking a massive public education campaign and if, after actually modifying the labeling on aspirin containers which reflects this concern that HHS has, they later, 6

months, 3 years, 10 years down the line, change their mind, reanalyze the data, listen to another point of view and conclude otherwise, would you be able to regain the confidence of those patients that are children you are treating for juvenile arthritis? Would aspirin be able to be rehabilitated and again used as you would like to see?

Dr. KLEIN. I would say that it probably would take another massive reeducation program and as much publicity. I don't think you would get as much publicity on the other side of the coin afterwards. I think, though, that after many years it may be possible. I think in the meantime a lot of people are going to go through a lot of very difficult situations until the message is given out clearly as to what to do.

Mr. SCHEUER. When you are dealing with professionals and you send them an advisory of some kind and then you reverse that 6 months or a year later, you have a controlled group of people whom you have informed according to one theorem; you can identify the exact group 6 months or a year later, they are professionals, they read medical advisories with confidence and sophistication and they can change rapidly. But when you have an explosion of publicity by radio, television and the press, addressing patients who are not at all sophisticated and who are filled with fear and foreboding in some fuzzy way about aspirin, to get back at them, it seems to me, really is an impossible job.

Dr. KLEIN. Yes.

Mr. SCHEUER. A very difficult job at the very least, not only to replicate the exposure, which is difficult over the mass media, but to get them to concentrate and to study whatever new knowledge has been adduced. And to tack that onto the fears and foreboding and anxieties that they have developed as a result of the prior burst of publicity, it just seems to me that is an extremely difficult job, far more difficult than adding on a bit to the postdoctoral education of the country's physicians.

It seems to me that where the Government undertakes to educate patients, they ought to make sure they are right and they ought to be sure in costs and benefits they have an overwhelming case for what they are doing.

I supported what Secretary Califano did in terms of educating patients inter alia, among other people in the whole population, about the dangers of smoking because there it was such a clear-cut issue it didn't beg any querulous dissent.

But here, where they may be filling patients with forebodings that will really result in harm, where patients of a very large patient group may have unscientifically based anxieties about giving their kids what is absolutely the most medically desirable treatment for their kids, the kids with rheumatoid illnesses of one kind or another, I think the Government should act very carefully and with great circumspection and based on very, very compelling data and case studies.

What you, as the third witness this morning, have told me along with the other two witnesses is that the data base on which the Government seems to be acting is seriously flawed, and I just wish that Secretary Schweiker were sitting with me here today.

They are fine men. Secretary Schweiker, as I mentioned before, is a man of exceptional character and intelligence. One of the witnesses mentioned he was not a doctor. Well, I am not a doctor, but I can read, write and count and reason cerebrally, and Secretary Schweiker surely is capable of doing that and he is surely capable of absorbing information in a very sophisticated, highly thoughtful way.

I fear that he has not been done justice by the people who have been designated to advise him and that the data base on which they are acting and on which they are making value judgments, I fear that that data base has been flawed and that, therefore, the advice they have given Secretary Schweiker has been flawed and that therefore this massive government intervention may in the end do far more harm than good.

You can be sure that your views and the views of the other witnesses will be made available to the Department. We will send this down to the Department as soon as the transcripts are completed, and hopefully they will crank this into the computer and make what is apparently an emerging consensus to part of their decision-making process, for which I fervently hope.

Our aim in holding these hearings is not just to create divisiveness and unpleasantness. Our goal is to make a constructive contribution to the decisionmaking process down at the Department of Health and Human Services.

I thank you very, very much for your testimony, Dr. Klein. It has been most useful, as has the testimony of the two witnesses before you, and the public is grateful to you too. Thank you very much.

Dr. KLEIN. Thank you very much, Mr. Chairman.

Mr. SCHEUER. We will now hear from the next witness, Mr. Paul Hinson, executive director of the American Reye's Syndrome Association.

Thank you for being here, Mr. Hinson. We have your testimony. We suggest that you take 8 or 10 minutes and give us the highlights of your testimony and, in addition, any other observations you care to make about anything you have heard this morning. Please proceed.

**STATEMENT OF PAUL HINSON, EXECUTIVE DIRECTOR,
NATIONAL REYE'S SYNDROME ASSOCIATION, DENVER, COLO.**

Mr. HINSON. Thank you, Mr. Chairman. We have heard from some of the professionals to this point from the medical field. I myself am not a physician nor am I an epidemiologist. What I am is a counselor and gatherer of information and full-time executive director of a new parent organization. This organization represents several hundred families who have suffered from Reye's syndrome.

I would like to repeat some of the things which have been said this morning in terms of the observation we have made as a lay organization. I believe that our observations do agree very much. They agree very much with what has been said this morning.

Genuine Reye's syndrome is usually fatal when not diagnosed and treated in the early stages of the disease.

What the actual fatality rate is is almost impossible to say with the statistics available today because epidemiology does not have

the tools at this point. There is not an easy diagnostic test that every clinic can use and say, "This is Reye's," or "This is not Reye's."

There is even a discrepancy on the level of diagnosis among the major treatment centers.

Based on death reports alone, Reye's seems to be the most common hepatic cause of death in children in the United States. It continues to be a medical mystery. There is no known cause, and the mechanism of the disease is not understood. We have at our disposal neither a cure nor any dependable means of prevention at this time. The best preventive tool that we have in hand is education of patients and of the health care providers in the early recognition of the disease.

That is the major focus of our association at this point, because we believe that early detection and supportive management can save most of Reye's syndrome patients. I am speaking of genuine Reye's syndrome and not confused with Reye's syndrome-like syndromes, and so on. The recent epidemiological studies and the subsequent public announcements concerning the possible implication of salicylates in the etiology or aggravation of Reye's syndrome is really a mixed blessing for us as an organization.

It will both help and hinder our efforts to create and provide an effective early recognition program. They have helped in the sense that they have awakened interest in the disease among the medical community and Government agencies and as well as kind of a vague recognition of the name Reye's syndrome among the general public.

The hindrance comes because of the closed minds of those who jump to conclusions. Among the general population, I think that would be a lot of people.

We have encountered a surprising number of people since February of this year who have resisted actively learning the early warning signs of Reye's. They remember the headlines like "Aspirin Linked with Reye's," and "Government Links Aspirin to Fatal Childhood Disease." That is what the majority of the people remember.

Mr. SCHEUER. Let me ask you, if I may, why should Government linkage of aspirin with a fatal childhood disease make parents reluctant to identify the early warning signals of Reye's syndrome? It seems to me they would even be more eager to identify early warning signs of Reye's syndrome so that it could be nipped in the bud, perhaps, without using aspirin.

Mr. HINSON. What we have observed is that they tend to make a medical conclusion from the headlines, which is about all they have time to see, or the brief statement made on television which does not plug it into a whole context but speaks only of aspirin and Reye's.

Reye's being relatively uncommon, most people have no idea what it is or what is involved or what could be involved. So when they hear the announcement "Government Links Aspirin" to this thing, there is an automatic transition in mind that says, "Well, that must be the thing. We don't know about Reye's, therefore it must be caused by aspirin and therefore if we don't take aspirin we won't get Reye's" is the assumption.

So we approached them with our awareness material. They said, "Reye's syndrome? Oh, I heard that, that is the thing you get from taking aspirin. I don't need to know that because we don't give our children aspirin anymore."

This is the kind of response which has built our concern about the actions which have taken place today. And at the time the announcements came out—we have a advantage in the Rocky Mountains of knowing whether the news is coming on the air because it has already been aired here, and so each time something was to be announced on television in Denver we called to the stations and had them put a number on the screen when the announcement was made and therefore offering our services to help field some of the questions.

Mr. HINSON. I concur with the experience of the doctors here. The calls that came as an alarm are amazing. After the caution was given out in February on the evening of the 11th before a holiday, we had a number on and this was the first of the announcement. We do not have a multiline system, and we covered 500 calls in 48 hours from that announcement. Basically all of them concern a virus and we have been giving them aspirin, what is going to happen to them? And another negative result of these warnings that I witnessed personally was a laying on of very heavy guilt trips with parents who had recently lost children to Reye's syndrome. Again the problem was down to two conclusions. For some reason, Reye's syndrome grieving is riddled with guilt, as in many other causes of death.

Mr. SCHEUER. Would you repeat that sentence?

Mr. HINSON. In Reye's syndrome, our experience has been that parents who have lost a child to Reye's, in their grieving process, they are very much burdened with guilt, that there was something that we could have done or should have done and did not do. And in some ways it is like an accidental death, in that there is usually no chance to say goodbye. The child is in a coma before they know what it is, and if he does not come to, there is no chance to say goodbye. It is also in a sense like a murder in some ways. The parent feels they are at fault. It is unreasonable, but they lay that upon themselves sometimes.

And so take some instances of children who died early this year at the end of the previous year, people who had not had a chance like other members of the association to really absorb the total picture of Reye's syndrome, and were still viewing it maybe in just bits and pieces, and who are in a state of grieving. Then the Government comes out and says, a very strong authority figure, says you gave your child aspirin and he died, in effect. And it does not matter that that might just be coincidence or that they did not know; they have been convicted. I do not want to overemphasize that area, but I have spent many hours counseling with parents in this type of trap this year.

I am not going to attempt in any way to evaluate the studies themselves, but simply to say that I am personally familiar with about 130 cases of diagnosed Reye's syndrome and many others that are Reye's-like, and I am also familiar indirectly with other groups of cases—none of them, by the way, come from Ohio or Michigan—about 25 percent who have no recall of salicylate usage

prior to the onset of Reye's syndrome, and 75 percent who may have used salicylates, aspirin, in treating the viral onus that they have had was not seen to me to be of any significant variance from the averages of salicylates across the board. I also see no correlation between the dosage used and the severity of the Reye's—some stage 1 cases in relatively high salicylate usage, and some fatal cases.

As for laboratory findings, elevated serum salicylate levels may sometimes be found but may well be the result of the syndrome rather than the cause in any way. This has been brought forth by many.

Something of interest too that I noticed, the geographic distribution of all the cases I am aware of raises some definite questions. The majority reside outside the inner city. They reside mainly in the outer suburban/rural areas, and we have seen several inner city cases. The interesting feature about them was that almost all of them had been out of town during the 2 weeks preceding the onset of Reye's syndrome. It seems to me something other than aspirin must account for that.

Also, there are some areas that have very high incidence compared to the rest of the country. An example that I am most familiar with is Las Cruces, N. Mex., not a large town, but about three to four times higher incidence than I have seen in Ohio and Michigan studies per population base. There must be other areas like that, where they tend to appear in clusters, even when it is not a period of viral epidemic. That is basically what I would like to say that has not been said.

[The prepared statement of Mr. Hinson follows:]

Statement of Paul A. Minson

American Reye's Syndrome Association

September 17, 1982

Two things I want to clarify before making any observations on Reye's Syndrome or on the current aspirin issue: (1) what I am not (2) what I am. I am not a physician, epidemiologist or statistician, and I am not a parent of a Reye's Syndrome victim. What I am is a counselor, gatherer of observations, and full-time executive director of the American Reye's Syndrome Association representing several hundred RS families. I have been trying to piece together the overall Reye's Syndrome picture for almost three years.

Genuine Reye's Syndrome is usually fatal if not diagnosed and treated in the early stages of the disease. What the actual fatality rate is almost impossible to determine with current statistics. We could say 30 percent, based on cases reported to the CDC; or we could say 60 percent of RS cases are fatal if we exclude all cases which are of a mild form or don't fit the definition in every detail. Or we can go to the opposite extreme and claim a ten (10) percent fatality rate by estimating numbers of mild cases that may be going undetected or unreported. What I'm saying is NO ONE KNOWS. The tools needed for adequate epidemiology of Reye's Syndrome are not available, and will not be available until a uniform diagnostic test can be discovered to settle the confusion over what is RS and what is not RS. Reporting needs to be made uniformly from all areas, etc.

Based on death reports alone, RS seems to be the most common hepatic cause of death in childhood in the United States, yet it continues to be a medical mystery. There is no known cause, and the

mechanism of the disease is not understood. Therefore, there is neither a cure nor any dependable means of prevention at this time. The best preventative tool we have in hand today is education of parents and health care providers in the early recognition of the disease. Early detection and supportive management beginning at the earliest stages of the disease could save most RS patients.

The recent epidemiological studies and subsequent public announcements concerning a possible implication of salicylates in the etiology or aggravation of Reye's Syndrome are a mixed blessing. They have both helped and hindered our efforts as an Association to provide an effective early recognition program. The help is an awakened interest in the disease among the medical community and government agencies as well as a vague recognition of the name "Reye's Syndrome" among the general public. The hindrance comes from the closed minds of all those who jump to conclusions-- (among the total population that represents a lot of people). We have encountered a surprising number of people since February of this year who have resisted learning the early warning signs of RS. They remembered the headlines: "Aspirin linked with Reye's", "Government links Aspirin to Fatal Childhood Disease", etc. The headlines and one line announcements are what the majority remember. The headlines give an easy solution to the individual who is not familiar with the disease. In the case of Reye's Syndrome, the unfamiliar individual represents a majority of the population. At the mention of the name "Reye's Syndrome" we now get responses like: "Oh, that's the disease you get from taking aspirin. I don't need to bother about that -- we don't give our kids aspirin." I would like to do a random survey to determine a probable percentage of the population who are thinking this way, and plug the results into a formula for "confused information" as

as a risk factor in the outcome of Reye's Syndrome. How people can jump to the conclusion that avoiding aspirin in children will prevent Reye's Syndrome is easy to understand: (1) not many people are familiar with RS and even fewer have any idea of the possible factors that could be involved in the etiology of RS. (2) Association was implied (at least in reporting emphasis) with one item of voluntary exposure (aspirin) in the context of responsible concern (parental care of child). That is easy to remember and a simple solution, and all there is time for in a hectic schedule. This would not be as great a problem when dealing with more commonly known diseases and within the context of items of involuntary or unconscious or habitual exposure, e.g. cancer and one of the many suspected agents. Very few would conclude that avoiding smoking would prevent all cancer, because almost everyone knows of non-smokers with cancer.

Another negative result of the aspirin warnings earlier this year was the laying on of very heavy guilt trips in some parents who had recently lost children from RS. Again the problem was jumping to conclusions. For some reason RS grieving is riddled with guilt in almost every case. It is like an accidental death in that there is usually no chance to say goodbye. It is also like murder in some ways in that a parent feels they are somehow at fault. Then when the "government" (the authority figure) says you gave your child aspirin and he died, it doesn't matter that that might just be coincidence or that they didn't know-- they've just been convicted. I don't want to overemphasize, but I have spent many hours this year counseling with parents in this type of trap.

I am not going to attempt to evaluate the epidemiological studies that have been conducted. That is someone else's field of expertise. I am personally familiar with about 130 cases diagnosed as Reye's Syndrome and many others which were Reye's - like. I am also familiar indirectly with other groups of cases. None of them come from Ohio or Michigan. Over 25 percent have no recall of salicylate usage prior to the onset of Reye's Syndrome. Some treatment centers have reported even less. 75 percent does not indicate to me any significant variance from the average usage of salicylates across the board for treatment of similar antecedent illness. I also see no correlation between dosage and severity of RS. Some stage I cases had relatively high salicylate usage; some fatal cases had received none. As for laboratory findings: elevated serum-salicylate levels may sometimes be found, but may very well be the result of the syndrome rather than a cause.

The geographic distribution of all the cases I am aware of also raises questions. The majority reside in outer suburban to rural areas, and the inner city cases usually were out of town within two weeks preceeding onset of Reye's Syndrome. Something other than aspirin usage must account for this.

Besides the common element of contact with the rural environment which may suggest various toxic elements peculiar that environment, some local areas seem especially prone to a higher incidence of Reye's syndrome.

Cases occur in every month of the year, however there is generally an increase in incidence during the winter months. This would indicate that viral activity has a primary role to play in development of the syndrome. So far at least 19 different viral agents have been identified

in conjunction with viral infections preceeding the onset of RS.

The age range is primarily 3 to 19 years, however there seems to be an increasing number cases being recognised outside that range, especially among infants whose symptoms are different from the older groups. The youngest: 2 months; the oldest : 57 years.

In summary: Reye's Syndrome presents us with a large set of possible combinations of etiological factors and remains an enigma. The first logical step in unraveling the mystery seems to me to be extensive public education in early recognition of Reye's Syndrome and similar fatal syndromes. Besides the immediate effect of saving lives, early recognition of enough cases is necessary to open the doors to better epidemiological tools for RS, as the possibility well as of more laboratory involvement. Much basic research is also needed. When the viral/host interaction is understood in Reye's Syndrome, we will be on the road to understand the roll of virus in many other diseases which are much more common.

Mr. SCHEUER. Well, thank you for your testimony. I take it as a counselor you feel that parents of children suffering from flu or chickenpox should be made knowledgeable and should have their level of consciousness raised on the early warning signals for Reye's syndrome.

Mr. HINSON. Yes, we do, very much so.

Mr. SCHEUER. I take it you feel that this is true whether or not the child is on any medication or no medication?

Mr. HINSON. That is right.

Mr. SCHEUER. So I take it you feel that—you have reservations about the Government singling out one medication as the culprit when there is no credible objective data base indicating a cause-and-effect relationship between any one medication and Reye's syndrome as against all other medications or no medication?

Mr. HINSON. Yes, especially in this situation where it is such an unknown disease among the general public's knowledge.

Mr. SCHEUER. What would you recommend as a program for parents to enhance their level of consciousness about the importance of identifying the early warning signals of Reye's syndrome early in the process, early in the game?

Mr. HINSON. Our approach is to try to present the information of what to look for whenever a child has a viral illness, especially flu or chickenpox, which seems to be the predominant period for watching, and we try in our literature, our handouts, not to create any cause for panic, but simply to be aware if your child begins to suddenly vomit unexpectedly and repeatedly after he is getting over a flu or something, a red flag should go up, and check with

your doctor right away. That may run some risk of creating more calls into doctors' offices than need be. However, we feel that the way our literature is presented, it shows a combination of things that people can say, oh, wait a minute, that is no reason to get alarmed yet, until they see following upon that—you know, there is a considerable behavior change. Suddenly their child is acting very confused or very combative, not the way he would normally act in any other situation they have known.

Mr. SCHEUER. Mr. Hinson, as the Department of Health and Human Services got involved in this matter of the association of Reye's syndrome and prior aspirin use, did they ever contact the American Reye's Syndrome Association, you or any of the doctors who are playing a leading role in your organization, to get your viewpoint on what they contemplated doing?

Mr. HINSON. Not that I am aware of, neither us nor the national foundations which are the parent groups.

Mr. SCHEUER. Which national foundations?

Mr. HINSON. There is a National Reye's Syndrome Foundation based in Ohio and one based in Michigan, and then the American Reye's Syndrome Association based in Denver. They spring up all over.

Mr. SCHEUER. To the best of your knowledge, the Department of Health and Human Services people did not make contact with any of you or any of the doctors associated with you to ask——

Mr. HINSON. Right. As far as we know, they did not.

Mr. SCHEUER. Thank you very, very much for your testimony.

Mr. SCHEUER. We will now hear from Mr. Frank Hurley, president of the Biometric Research Institute of Arlington.

We are happy to have you, Dr. Hurley. We have your testimony. We would ask you to sum up, to hit the high points in about 8 or 10 minutes, and please feel free to refer to anything that may have aroused your interest this morning.

STATEMENT OF DR. FRANK HURLEY, PRESIDENT, BIOMETRIC RESEARCH INSTITUTE, ARLINGTON, VA.

Dr. HURLEY. Thank you, Mr. Chairman. I am pleased to have the opportunity to discuss the relationship of salicylate use and Reye's syndrome. Since 1972 I have been on the faculty of Georgetown University, division of biostatistics and epidemiology. Prior to that I was on the faculty of George Washington University. In the 11 years since we were founded we specialized in the design, monitoring, and evaluation of health research, both clinical trials and epidemiologic studies. We were retained by Sterling Drug and Schering-Plough in mid-June to undertake an independent audit and analysis of data from the Ohio Department of Health study of Reye's syndrome. Our conclusion of that review is that the results of the second year of the study do not provide sound statistical evidence of any association between salicylate use and Reye's syndrome.

Mr. SCHEUER. Would you repeat the beginning of that sentence?

Dr. HURLEY. The conclusion of our review of the Ohio study——

Mr. SCHEUER. Both the first and second year?

Dr. HURLEY. Our review concentrated on the second year, but the basic conclusion of the review is that there is no sound statistical evidence indicating an association between salicylates and increased rate of Reye's syndrome.

Mr. SCHEUER. No cause and effect?

Dr. HURLEY. Yes. I would like to review the background of our review, the scope and the reasons for that conclusion.

As background, repeated requests on the part of the pharmaceutical manufacturers for the raw data have been made since November 1980. This culminated in release of the data in June of 1982 as a result of a lawsuit brought by Schering-Plough. The raw data as you probably know from our perspective in reviewing the study, the raw data are the original records collected at the time that the cases and controls are interviewed, as well as the data relating to the medical condition, the results of the blood tests and so on that are used to diagnose cases of Reye's syndrome. Raw data is necessary for the evaluation, since it is the foundation for any analysis and conclusions drawn from a study.

The scope of our review, although there were other studies done on Reye's syndrome, we focused on the second year of the Ohio study because the second year of the Ohio study is the only study that provides the information necessary to assess the relationship of aspirin use and the onset of Reye's syndrome. This is a crucial issue in assessing the question of whether or not use of salicylates is associated with an increased risk of Reye's syndrome.

As an example, certainly everyone will recognize that use of salicylates is very much associated with headache. However, in that instance it is clear that the use of salicylates does not cause headache, it is used to treat headache. There is substantial evidence in the data that salicylates are used to treat symptoms of Reye's syndrome, and so therefore this use to treat Reye's syndrome could clearly result in an apparent association.

Mr. SCHEUER. This is one of the classical fallacies that we learned in our college ethics or philosophy courses, the post hoc ergo propter hoc fallacy. After it, therefore because of it. You are saying it may be after it, but that does not mean that it is caused by it.

Dr. HURLEY. In this instance it may not even be after it, and that is why we needed the raw data. As the FDA noted, and I will quote from their task force report delivered on the 18th of May this year, it was considered critical that use of aspirin must have been before the onset of Reye's syndrome to be considered true exposure, and also, the 64 cases and the 110 controls, that is the second year Ohio study, were the only data that provides this information. The other studies and also the first year of the Ohio study did not provide information on daily symptoms and daily aspirin use. They looked at an overall indication of medication use and an overall presence of symptoms, so it was very difficult to determine where Reye's syndrome actually started as opposed to the antecedent illness, and when was the aspirin given, was it given in association with the

illness or given after the illness had started to treat symptoms of Reye's syndrome.

Although a number of people indicated potential biases, and a lot were discussed at meetings, it was impossible to assess the magnitude of the impact of those biases on the results without reviewing raw data. These biases include misdiagnosis, problems with medication history, differential case-control recall.

I think that it is a well-known issue in case control studies that medication histories are recalled very differently by cases than they are by controls. This is exacerbated in the Ohio study by the fact that cases were interviewed in a hospital where there is very little possibility of prehospitization medication. When the controls were interviewed in the home, there was a possibility of reviewing the medication to confirm what medication was given. The question of comparability of risk, were the cases and controls suffering from the same types of viral illnesses, were the severities of those viral illnesses equivalent? The most important question that required the raw data was the temporal relationship, was the aspirin given before or after Reye's syndrome had started?

Mr. SCHEUER. Even if it were given before, that in and of itself would not necessarily be probative of anything?

Dr. HURLEY. That is true, but certainly if it was not given before, that is conclusive that it was not positive. The objectives of phase 1 of our review was to examine the second year of the Ohio study, to address the question of misdiagnosis, to audit the raw data on medication histories, and to analyze the data based on the definition of exposure, that aspirin exposure must precede the onset of Reye's syndrome. In phase 2, currently underway, comparing cases and controls for severity and characteristics of the antecedent illnesses and to determine if the treatment differences are in fact explained by differences in symptoms, which we have noted.

Our findings, as alluded to earlier, particularly by Dr. Eichenwald, there was an extremely low rate of biopsy confirmation relating to the question of misdiagnosis of cases, an extremely low rate of biopsy confirmation, and extremely low rate of identification of viral agents. Only 18 percent of cases had the viral agent identified through serology or clinical confirmation. In 8 percent of the cases, there was clinical confirmation of chicken pox. Most importantly I think as referred to by Dr. Eichenwald, the death rate of the cases in Ohio is completely atypical of what one would expect for Reye's syndrome. In a disease, even in the best of circumstances, where mortality is reduced to 15 to 20 percent, the likelihood of finding a death rate of 4 percent, as we saw in Ohio, in 194 cases is less than 1 in 10,000.

Mr. SCHEUER. Excuse me for interrupting you. To what do you ascribe that remarkable deviation from what could have been statistically projected?

Dr. HURLEY. The only possible explanation is in fact misdiagnosis.

Mr. SCHEUER. And that an awful lot of cases were diagnosed as Reye's syndrome that in actuality could not have been Reye's syndrome?

Dr. HURLEY. Exactly. That is an important perspective. A number of people might say that misdiagnosis would tend to dilute

association rather than introduce spurious associations. However, there are a number of instances such as accidental salicylate overdose which could be diagnosed as Reye's syndrome, obviously including acetylsalicylate overdoses. Reye's syndrome would certainly introduce that spurious association.

With respect to medication histories, in a study during the second year of the Ohio study, the case reports were modified to collect information specifically on day-by-day medication used, because at that time the Ohio Department of Health had postulated that in fact Reye's syndrome was related to medication use. Certainly one would expect that in those circumstances the medication histories would be very carefully done. In fact that was not the case. In 22 percent of the cases and in 17 percent of the controls, medications as reported or the names of medications as reported on the case report form were such that one could not tell which of several different formulations had been used. As an example, Congespirin was written with no designation as to whether it was liquid or tablets. One form contains acetoaminophen; the other form contains aspirin.

In four cases and in three controls that was critical, because the medication listed was the only possible salicylate exposure for the case or the control.

In the third area of our review, when we did the analysis comparing aspirin use in cases and controls, when we define aspirin exposure as aspirin exposure preceding the onset of Reye's syndrome, we used two approaches outlined by FDA in the report, one of which they noted in the May 24 meeting. However, they were unable to complete the analysis of the data, the section referring to table 5 of their report, and I believe it starts on page 49 of their report. In that instance they had identified 41 out of 64 second-year cases in which they felt that the use of aspirin relative to the onset of Reye's syndrome could be determined with reasonable certainty. That is, they were able in those cases to determine whether or not aspirin had been used before Reye's syndrome started or after Reye's syndrome started. In those 41 cases, 7 of the 41 did not use aspirin until Reye's syndrome had started. This results in no statistical significant association between aspirin use and an increased risk of Reye's syndrome. The association is further weakened when one considers that in four additional cases in addition to those seven, the medication—it is unknown whether or not the medication given to the child contained aspirin or not.

In the second approach outlined by FDA in their May 18 task force report, they had eliminated 16 of the 64 cases who had developed Reye's syndrome in the first 4 days of the antecedent illness. They eliminated those people because they felt there was a likelihood that in fact Reye's syndrome was present on the first day. Again we analyzed the data using the conditional logistic model and we found no statistically significant association between aspirin use and increased risk of Reye's syndrome. When the FDA did the analysis, when they looked at aspirin use on day one only, they found that in fact it was a statistically significant association. FDA found when they looked at aspirin use on day one only—

Mr. SCHEUER. Day one of the outset of Reye's syndrome?

Dr. HURLEY. On day one of the antecedent illness compared to day one of the corresponding illness for the control, they found a statistically significant association. However, it seems to us that the issue is not whether or not cases took aspirin sooner. I think that there is a fairly clear indication from the date of agreement by most people with an opportunity to review it that the illness for the cases are somewhat more severe than for the control, and under those circumstances it does not seem unlikely that on the first day they might have medicated sooner than a control with a minor illness. That is the issue that FDA goes to, when they look at day one or two only, did the cases use aspirin sooner than the controls, not the question of did aspirin lead to an increased risk of Reye's syndrome.

In order to do that question you need to look at the entire period of the antecedent illness for the cases and the entire period of the corresponding illness for the controls. Even when we threw back in all the cases for which we could not make a determination whether or not aspirin use preceded onset of Reye's syndrome, some of the cases where Reye's syndrome developed on the second or third day of an antecedent illness, we found that the statistical significance of the association is highly dependent on the assumptions you make about those medications which on the basis of the case reports you cannot tell whether or not they contained aspirin, referring back to the Congespirin.

Those are the basic findings of phase 1 and phase 2 to date. We have said we are proceeding with the analyses of those data, comparing the symptoms for cases and controls to do a more specific job on the comparability of the illness, the antecedent illness in cases and the illness in controls. We expect to find out of that—we already know that there is a substantial difference in the types of diseases that cases and controls had. Controls had a substantially higher incidence of GI symptoms than cases did.

Mr. SCHEUER. That is gastrointestinal?

Dr. HURLEY. Yes, gastrointestinal symptoms than cases. We have not completed our analysis of the data, but it is possible that given the fact that acetoaminophen is widely advertised as being safe in the face of gastrointestinal upset, this is what causes reverse association, the fact that in some 40-plus percent of the controls there was associated GI upset and in only 23 percent of the cases was there associated GI upset.

[The prepared statement of Dr. Hurley follows:]

STATEMENT BY FRANK L. HURLEY, PH. D., VICE PRESIDENT, BIOMETRIC RESEARCH
INSTITUTE, INC. (ARLINGTON, VA.); REYE'S SYNDROME AND ASPIRIN USE

Biometric Research Institute, Inc. (BRI) recently performed an independent audit and analysis of the raw data of the Ohio Department of Health (ODH) Case-Control Study of Reye's Syndrome (RS). The conclusion from BRI's review is that the results of the pivotal second year Ohio survey do not provide sound statistical evidence that the use of salicylates increases the risk of Reye's Syndrome. The basis for this conclusion is described in detail in the attached report and outlined below.

BRI is an independent research organization formed in 1971. BRI specializes in the design, monitoring and analysis of health research. Our clients have included the Veterans Administration Cooperative Clinical Studies Program, the National Academy of Sciences, and the National Institute on Drug Abuse as well as a number of major U.S. Corporations.

BRI was retained by Sterling Drug Inc. and Schering-Plough in mid-June 1982 to undertake an indepth independent audit and analysis of the raw data. Raw data consists of all primary material obtained by study investigators during the data collection phase of a study, and the importance of careful review and analysis of raw data cannot be overemphasized. Simply put, a house with a poor foundation will fall. It is my understanding that, despite repeated requests by aspirin manufacturers from November 1980 to June 1982, it was only by court order in June 1982 in a suit brought by Schering-Plough against the State of Ohio that ODH released the raw data for independent scrutiny. At that time raw data from the Arizona and Michigan surveys were not similarly available for outside review.

BRI decided that the most appropriate review of the raw data of the three RS surveys would be one that concentrated on the second year Ohio survey, since (a) it was the largest of the three state surveys and more importantly (b) it was the only survey with the critical

information needed to assess the temporal relationship between the use of aspirin and the onset of RS. With respect to this latter point, of all RS surveys completed to date only the second year Ohio survey has records of daily symptoms of subjects, which allow a determination of when RS began, and records of daily drug usage, which allow a determination of when aspirin or other salicylates were used relative to RS onset. According to the May 18, 1982 report of FDA's RS Working Group:

"It was considered critical that the use of Aspirin must have been before the onset of Reye's Syndrome to be considered true exposure."

and

"The 64 cases and their controls (i.e., the second year Ohio survey), totaling 164 individual reports, were the only data that provided this information." (FDA RS Working Group Report, page 31, lines 11-13, 14-16)

BRI agrees with FDA that this general epidemiologic principle is a cornerstone of any analysis of the recent RS surveys.

The major findings by BRI are:

- (a) misdiagnosis of RS was likely such that a number of subjects (estimated at 27%) did not have RS;
- (b) there was no confirmation of medication histories (i.e., there is no record that interviewers visually identified the bottles of medications which were recalled as being used);
- (c) in those cases for whom the timing of aspirin use relative to RS onset could be determined with reasonable certainty, aspirin use by cases was not significantly different from controls; that is, no statistically significant association exists;

- (d) substantial product confusion exists in identification of specific formulations of fever reducers and the Ohio Group used an arbitrary one-sided assumption in assigning a designation of "aspirin use" to a critical number of subjects for whom it was, in fact, unknown whether they had used aspirin; as shown in the attached report product confusion can account for the claimed association;

In sum, the demonstration of substantial biases in the pivotal second year Ohio data establishes the questionable nature of the data. Consideration of the problems of misdiagnosis, the temporal relationship of salicylate use relative to RS onset, and product confusion leads to the conclusion that the RS surveys were seriously flawed to the extent that it cannot be concluded with any degree of confidence that salicylates place children at excess risk of developing RS.

Mr. SCHEUER. Your testimony has been very, very interesting, and this is a very interesting description of the Ohio study. I take it—well, let me ask you this. Could you have come to your findings on the Ohio study that you have just given us without having access to the raw data in the individual case reports?

Dr. HURLEY. No; you could not. As I mentioned, there were a number of things, avenues of investigation that we pursued that it was absolutely essential to have the raw data, certainly to audit the medication histories and to look at the timing of aspirin exposure relative to onset of disease.

Mr. SCHEUER. Do you think that any first-rate scientist without access to the raw data in the case reports could draw reliable and thoughtful and professional conclusions from the Ohio study?

Dr. HURLEY. The only conclusions that could be drawn or the only question that could be addressed in that instance is whether or not aspirin is associated with Reye's syndrome in the same sense that aspirin is associated with headache, not with regard to whether aspirin is associated with increased risk. You need to know whether or not the aspirin use preceded the onset of Reye's, and in order to address that question, you have to have the raw data.

Mr. SCHEUER. All right. Our majority counsel, Jonah Shacknai.

Mr. SHACKNAI. Let me ask first, do you believe that you have in your possession now or at least have access to all the raw data and the case histories of the Ohio study?

Dr. HURLEY. No; we do not. I believe that there are really four areas that we would like—where we feel there is data missing.

Mr. SCHEUER. That has not been released.

Dr. HURLEY. That has not been released.

Mr. SCHEUER. By CDC?

Dr. HURLEY. By Ohio and/or CDC. We would like a complete accounting of all cases of Reye's syndrome reported to the Ohio De-

partment of Health during the study period. We have received information from Dr. Orlewski [phonetic] at the Cleveland Clinic in Ohio, who was one of the original investigators, that in fact a number of his cases were unaccountably dropped from the study and not included in the final report. He has also indicated in the 11 cases he had, ranging over 1971, some—1979 up into early 1981, that in the 11 cases of Reye's syndrome that he diagnosed at the Cleveland Clinic, aspirin use preceding Reye's was only 50 percent, substantially different than that reported by the Ohio Department of Health. A number of those cases apparently have been excluded from the study for one reason or another, and he does not know what those reasons are.

Mr. SCHEUER. Do you have any suggestions as to what those reasons might be?

Dr. HURLEY. We just found this out and it is a very, very troubling issue. Certainly we would like to know how many other cases were reported that for one reason or another, were dropped. We would like to look at the data on those cases.

Mr. SCHEUER. Well, we hope to make that possible for you.

Dr. HURLEY. There are three other areas we would like to look at. I think that Dr. Eichenwald mentioned earlier on the question of misdiagnosis, he reemphasized the chances of this group of 194 cases all having Reye's syndrome is less than 1 in 10,000. Even if you cut the number down, the chances of them all being Reye's syndrome is very small. We would like to look at all the hospital records, the admission reports on each of the children, the lab tests that were done at the time of the admission, the treatment course for the children, to be able to assess if in fact the data that was collected in the hospital, the complete laboratory profiles, the blood chemistries and so on, in fact support the diagnosis that Ohio has made of Reye's syndrome. We have received from CDC in response to a request—they took some time to respond to it because they said their records were not well organized in terms of being able to pull out the Ohio data. We asked for the CDC forms on all the Ohio children. We have received some of those, but they have removed identifiers so there is no way for us to link any form to the corresponding questionnaire from Ohio. We would like to see the case numbers attached to the reports so in fact we can use those data. Right now they are useless to us.

In the final area, we would like to see any notes made at the time of the interview or at the time of the data collection process for each case. You can imagine the notes that an interviewer might make indicating potential uncertainties by the parents about symptoms would be crucial in evaluation of the data and we do not have those.

Those are the four things that we would like to see.

Mr. SCHEUER. We will certainly confer with you and do what we can to fill the gaps in the data base with which you have to work.

Our distinguished subcommittee counsel, Jonah Shacknai.

Mr. SHACKNAI. Epidemiologists have told me and the subcommittee that case history studies are necessarily cumbersome and often imperfect, and that they often have to go on the best suggestive evidence they can find. In your opinion, is this study so egregiously

flawed as to not be worthy of consideration insofar as its statistical significance is concerned?

Dr. HURLEY. We have a number of very serious questions about it. I hesitate to say that there is any data around that is so bad it is useless, but certainly the questions relating to the misdiagnosis and the questions relating to the completely inadequate—what I feel are inadequate medication histories or controls on medication histories, bring this study close to that.

Mr. SCHEUER. Let me elaborate on that first question.

Nobody is suggesting that the work of the Department of Health and Human Services is useless or perhaps nobody is saying that the Ohio study is useless.

The question is, given the reservations that you and the other witnesses have voiced about the significance of the Ohio study and the doubts about the reliability of the data base, do you think that the Ohio study was sufficiently probative of a cause and effect link between the use of aspirin and Reye's syndrome and the child's having Reye's syndrome that it would justify this very significant and important and almost irreversible step that the Department of Health and Human Services is contemplating, namely, going public to patients around the world through the mass media, a step that is virtually irreversible?

Do you think the probative quality of that Ohio study would justify a step of this order of magnitude, a Government intervention of this order of magnitude?

Dr. HURLEY. Even if I were to say the quality of the study was good, the results contained in the data do not support that move. The results do not show any statistically significant association between use of salicylates and Reye's syndrome. To address the question of the quality of the study, the study was not necessarily specifically designed to address the question of salicylate use and Reye's syndrome.

In that sense the work may be a good study in the overall contribution of knowledge to the epidemiology of Reye's syndrome. However, I think it is unfortunate that a study that was not designed specifically with the very rigid types of controls you need on medication histories and so on should then be used for a purpose it was never intended for.

Mr. SCHEUER. Ms. Bach, our minority counsel.

Ms. BACH. Mr. Chairman, if I could, my question I would like answered by Dr. Hurley, and then if our other witnesses would like to comment, they may do so.

Mr. SCHEUER. Fine.

Ms. BACH. I am asking the question not from your knowledge of statistics but as a concerned citizen, and also because of your professional background.

Given the responsibility that HHS, FDA, CDC, and other Federal agencies that are charged with protection of the public health have, and given the fact there there have been situations where we have hammered on these agencies when they have received information from physicians that warn them of certain consequences of medication, and where they haven't followed through or where the public feels that they haven't followed through on the recommendations of physicians, is this present aspirin warning decision the

kind of situation where we are damning them if they did and damning if they didn't. Or, in your opinion, how should they have dealt with information that they received insinuating there may be some sort of relationship between a drug and a disease?

Dr. HURLEY. I think it is clear that there should have been a thorough review by independent parties of the actual raw data before they proceed to a decision. Those data were not available in fact until after that decision was announced.

Ms. BACH. Should they not have publicly seized any type of warning or what should they have done with information that they received before it was substantiated.

What should they have done with the information that they were receiving which indicated that there was some sort of association? Should they have withheld it? Was there some sort of communication that they should have taken place prior to the warning physicians?

To what degree should they have dealt with that information before a specifically designated HHS study was conducted, which in your opinion would have more properly addressed the relationship?

Dr. HURLEY. I think that, as I have pointed out, a review of the raw data indicates no significant association. And I understand the difficult policy issue for the agency in terms of what do you do when you only have scanty data. I think that that is a policy issue.

My point is, in terms of the scientific review of the data, we find no statistically significant evidence of that association, and in terms of the sequence of events, certainly I think that those data should have been made available to interested parties and, as has been suggested here, perhaps there could be an independent peer review group set up to review those data. I think that this is a very important public health decision.

You have heard other witnesses testify about the importance of aspirin as a product. That is something that is out of my field as an epidemiologist or a biostatistician in terms of discussing the clinical importance of aspirin, but you have heard others talk about that. It is obviously an important public health decision and to make that precipitously before making the data available I think was wrong.

Mr. SCHEUER. Before making the raw data and the case studies available to groups like yours?

Dr. HURLEY. Right.

Mr. SCHEUER. Or even made available for the internal consideration of the Center for Disease Control experts and the Department of Health and Human Services experts?

Dr. HURLEY. Yes.

Mr. SCHEUER. As well as outside experts like yourselves?

The Government's own review of this matter was flawed by not having the basic raw material of the case studies available to those researchers?

Dr. HURLEY. Yes.

Ms. BACH. Mr. Chairman, do you mind if our other witnesses comment?

My concern is, is that there is always a difference in interpretation when you are dealing with the American public, people who

are unfamiliar with the technical and medical implications. Versus the understanding of trained, licensed physicians.

I am wondering how physicians feel given a situation such as this, when information comes to a Federal agency which has an enormous impact on the American public. At what point should the agency say something and not be accused of withholding information? On the other hand, how does the Agency avoid unnecessary paranoia about something?

Is there anyone who wants to comment?

Dr. EICHENWALD. Actually, this sort of decision comes up all the time. The FDA I know receives reports continuously about possible toxic effects of certain substances, medications, and so forth.

And there is the FDA letter, which goes to all physicians in the United States with some regularity, which lists some of these concerns as concerns but doesn't draw any particular conclusion. And this particular information is also not widely disseminated among the public, because the public simply would not understand it.

For example, Tylenol is associated with liver disease if taken in excessive dosage and so individuals seem to be sufficiently susceptible to that effect that even with fairly reasonable doses they may have some problems.

Well, you cannot publish or publicize every possible toxic effect of every single substance that we use as medications as are used in agriculture without making the public totally confused.

I think the Government can act when there is sufficient basis for action, but not in instances where all that one is dealing with is a suspicion or a supposition, particularly with a medication which is widely used and which has very definite advantages over other agents in the treatment of diseases quite different from those that might cause Reye's syndrome.

I think it is a decision they make all the time, and that is why I was so surprised when this came out on the basis of less information than many other items that they have studied and have not made public pronouncements about.

Mr. SCHEUER. Dr. Johnson, Dr. Klein, do either of you wish to add anything?

Dr. JOHNSON. I would certainly—I would completely concur with Dr. Eichenwald.

I think as I see the community of general pediatrics, I think there is some concern on the part of the practicing pediatricians about the timing and the reasonability of the statement that was made by the Committee on Infectious Diseases of the American Academy of Pediatrics. Their faith has been shaken a bit because nowhere in their experience as practitioners have they seen this sort of association.

Mr. SCHEUER. Dr. Klein, have they spoken for you?

Dr. KLEIN. Yes; they have.

Mr. SCHEUER. Thank you very much, Dr. Hurley, for your splendid testimony. We are grateful to you.

We now have two witnesses left and we are running way behind because of the wonderfully stimulating testimony we have received, so I am going to ask the last two witnesses to make sure that they get through their affirmative testimony in no more than 10 minutes.

Dr. John Crocker, professor of epidemiology, Dalhousie University in Halifax, Canada. If you will give us an overview of your testimony and any reflections you wish to make on what you have heard today in 10 minutes to the second, we will then have some time to ask you questions, which we would very much like to do. So please proceed.

**STATEMENT OF DR. JOHN CROCKER, PROFESSOR OF
EPIDEMIOLOGY, DALHOUSIE UNIVERSITY, HALIFAX, CANADA**

Dr. CROCKER. I am an associate professor in pediatrics. As you may know, we have been involved with a large group of Reye's research personnel for about 10 years, having a fairly large group of urologists and toxicologists working on this particular entity. We have been looking at different chemical groups that are experimentally capable of causing Reye's syndrome.

Because of the rural incidence of this disease and the fact that when Dr. Reye first described the disease in 1963 he mentioned that a toxin was very likely pathological, we then began to look at our own cases and where they were coming from and, because many were in rural areas, we began to look at some of the pesticide ingredients that children are in contact with in rural areas and could not duplicate the disease with the pesticide itself, but some of the ingredients that make up pesticides, with them we were able to change the way influenza responds.

From a researcher's point of view there are certain basic steps that you have to have to have Reye's syndrome. The virus is fairly unique in Reye's syndrome in that when the child gets an infection he doesn't have an inflammatory response, no pus in the brain or liver. He has a virus response, but doesn't appear to have the normal reaction to chickenpox or influenza that you normally would get.

Also, we know that there is then a series of chemical events that go on within the liver and the brain. These children primarily die a brain death, dying from changes in certain organelles in the cell, the mitochondria which was blocked that are the main energy sources for the cell, and this is why you get a high serum ammonia. The ammonia in fact can reproduce many of the features of Reye's syndrome.

We have been struck by the fact that there has been a plethora of chemicals and agents known and being linked with Reye's, latex paints, aflatoxin, a series of chemical connections, and aspirin being one of them.

In fact, acetaminophen has also been linked in some publications.

The basic scientist studying Reye's then looks to see whether aspirin can cause Reye's syndrome, can you experimentally reproduce Reye's syndrome with aspirin? This has been tried in ferrets and we have experiments in another situation going which I do not have the results on yet, but basically, can you reproduce with aspirin and then exposing them to an influenza virus the same entity going on as you can with other chemicals?

The chemicals that we have currently developed a model on you can reproduce the liver enzymes, the fat changes, ammonia, the central nervous system death. This has not as yet to my knowledge

been reproduced experimentally. You cannot preexpose an animal and expose them to an influence virus—we have not been able to see that data forthcoming.

It is always nice when you have clinical data such as CDC has to then go back to the drawing boards and into the research laboratories and see, can you reproduce what you are seeing in a child experimentally, and that is one of the great concerns of the researchers that I have studied this with throughout North America.

Mr. SCHEUER. Apparently the CDC did not have the raw data and did not have all of the case records, and do not to this day have all of the case records, if I understand the prior witness, Dr. Hurley.

Is Dr. Hurley still in the room?

Dr. HURLEY. Yes.

Mr. SCHEUER. Dr. Hurley, did the CDC have the raw material and the case records in its possession at the time they did their analysis of the Ohio data?

Dr. HURLEY. No, they did not.

Dr. CROCKER. Whoever made the decision, I think, or whoever looked at the basic data, usually on an epidemiological study is indicative. I do not think it is the solid proof that a scientist would accept as cause and effect. You look to fulfill the hypothesis, if you say tuberculosis is caused by TB bacilli that you can take the bacilli and put them into an animal and get tuberculosis.

We have not been able to do that with aspirin. In contrast to my colleagues and other witnesses, I am not certain that aspirin has a complete clear bill of health. I worry that aspirin may slant the curve, that preexposure may slant the curve of severity. We know it has an effect on liver enzymes, that there may be a 20 percent movement of the mortality, morbidity curve, and that is only going to be available if we are able to use aspirin in some sort of an experimental situation. We can't preexpose children to aspirin and then expose them to flu virus, but you would like to have that basic science data which currently is not available, and that is where we are on very thin ice by coming out and hitting aspirin as the sole cause, which I think from the research data from around the world, aflatoxin and other agents can give the same entity, and I think the general public is going to be disappointed if aspirin is wiped off the market and we don't wipe out Reye's syndrome. They are going to wonder why wasn't basic work done first to back up the patterns that were thought to be present.

I will basically stop there and be open to any questions.

Mr. SCHEUER. Thank you very much, Dr. Crocker.

In your experience as a clinical researcher, is misdiagnosis of Reye's syndrome a comparatively common and frequent problem?

Dr. CROCKER. Yes. I see quite a number of cases of Reye's syndrome and there are many diseases that mimic Reye's syndrome. There are only a few groups in North America that actually demand a liver biopsy and having histological confirmation of their cases and this makes it very difficult to compare centers that do not go after tissue diagnosis, because then you are not sure whether you are dealing with one of the many inborn areas of metabolism that give you similar changes in the brain, high serum ammonia and many other of the features of Reye's.

I know it always seems a bit of an overkill to do a liver biopsy on something that sounds so severe, but you have to put the child's coagulation in shape and do a liver biopsy as part of the criteria.

Mr. SCHEUER. You think it is indispensable?

Dr. CROCKER. Yes. We think 30 percent of our data would not have been showing Reye's syndrome with a biopsy.

Mr. SCHEUER. How definitive do you believe the CDC's definition of Reye's syndrome to be?

Dr. CROCKER. I do not like to be unfair to CDC because I think they have done an excellent job trying to come to grips with the problem under a lot of public pressure. I think using clinical criteria, you would have to be—particularly if you are including—in Reye's syndrome you have five stages. If you are going to stage zero and one and calling those Reye's, that group is very shaky in my mind as Reye's syndrome unless you have a tissue diagnosis, and I think that there, because of the ambiguity of the diagnosis, they are in trouble.

Mr. SCHEUER. In the case of atypical clinical presentation, that is no vomiting, no behavioral change, no biphasic illness, could you be assured of an accurate definite Reye's syndrome diagnosis without the liver biopsy?

Dr. CROCKER. I do not think so. In atypical cases we recommend in the publications we have done to practitioners that liver biopsy in any ambiguous case, a liver biopsy is absolutely essential to that feature.

The other thing which hasn't been brought up is, where salicylate levels are done, are they really salicylate? That has been from the research point of view more so in that we know that a lot of the levels published as being salicylate poisoning, if you look at children's serum with no salicylate at all came back positive, and that is a little worrisome from the physician's point of view.

Mr. SCHEUER. Do you feel that one theory accounts for the causes of Reye's?

Dr. CROCKER. No. I think we will see that Reye's syndrome is multifactorial and there may be a different set of chemicals involved with varicella and different with influenza, and that may account for the regional differences we are seeing, if a conflict of Reye's syndrome proves to hold water as it is doing.

Mr. SCHEUER. Having said everything that you have said, how do you perceive them, the Department of Health and Human Services, their plan to require the labeling of aspirin?

Dr. CROCKER. Fortunately, Mr Chairman, that is a political decision. It is really very difficult.

Mr. SCHEUER. It is an important public policy decision.

Dr. CROCKER. One of the problems is of course that it may pay off in that it may change the severity of the diseases or it may actually cause a lot of harm in that arthritis is—children with arthritis and many other conditions who benefit from aspirin may not have availability to the drug.

I think it is a wise decision which, even though I am very close to the issue, I can sympathize with the Department of Health. I am not wholly committed that aspirin may not change the severity, and that is why I am not as committed to an absolute clean bill of health for aspirin as many of my colleagues.

Mr. SCHEUER. I do not think anybody here this morning has given aspirin a clean bill of health. I think there is a general consensus that more research has to be done, a general consensus that the basic raw material in the case studies must be available not only to the researchers but to the medical fraternity, yourself included, and that probably the decision to put the labeling requirement may have raced ahead of the validity of the data base, the depth of the data base, the availability of raw material, and the actual case-by-case data that would enable the medical fraternity, both in and out of Government, to make the very important public policy judgment to go ahead with the labeling.

I do not think anybody is criticizing the bona fides of the people involved in Government, whom I respect and admire enormously, but I think there is some feeling that the amount of raw material, the number of case studies available to the researchers, didn't justify the order of magnitude of the action contemplated at the time, and that the process, the whole scientific research scenario, had yet to unfold completely.

Dr. CROCKER. I think you are seeing it correctly. Really, I think the warning label rather than warning physicians may have been a bit of overkill.

Mr. SCHEUER. Yes. I think that is the feeling I am getting.

Dr. Crocker, thank you very, very much for your testimony. We appreciate it. It was very helpful to us. We appreciate your coming.

We are now up to our last witness, Dr. Reule Stallones, dean of the school of public health at the University of Texas, Houston. We are very happy to have you, Dr. Stallones.

You have heard a great deal of very interesting and provocative testimony today. We would ask you to give us an overview of your own testimony, plus any reactions you may care to give of what you have heard as you sat here very patiently listening to the prior witnesses.

STATEMENT OF DR. REULE STALLONES, DEAN, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF TEXAS, HOUSTON, TEX.

Dr. STALLONES. Thank you very much. I appreciate the invitation to appear.

I am Reule Stallones, dean and professor of epidemiology at the University of Texas School of Public Health.

I have begun to suspect I am a minority in this assemblance this morning which I trust will be a spiritually salutary experience for me.

Since the last time I met with some of my colleagues who have—

Mr. SCHEUER. We didn't expect you would be in a minority of one. We expected Dr. Brandt to be here too, so there would be a multitude of voices here.

We believe in letting a thousand flowers bloom. Yours will not be the only voice to take a particular position and we thoroughly expect Dr. Brandt will be down here in his own good time and we will have the benefit of his thinking, too.

Please proceed.

Dr. STALLONES. Thank you, sir.

Mr. SCHEUER. I just want to reiterate it was not our intention that you be standing alone.

Dr. STALLONES. Since the last time I met with some of my colleagues who testified this morning, at that time they were in the minority, perhaps this is only fair.

I was cochairman with Dr. Richard Johnson of Johns-Hopkins of a public meeting on Reye's syndrome sponsored by the Food and Drug Administration, the CDC, and the National Institutes of Health on May 24, 1982, alluded to previously this morning.

The meeting was attended by scientists engaged in research on the association between salicylate use and Reye's syndrome, representatives of and consultants to drug manufacturers concerned with the problem, and a group of scientists knowledgeable in these fields of research, but not identified with each of the other two classifications.

The meeting was arranged for presentation and discussion of research and was not planned to yield anything like a committee report of findings and conclusions. However, Dr. Johnson and I were asked and at the same time had to summarize the opinions expressed, especially those of the nonaffiliated participants.

During the course of the conference, the full array of opinions possible was expressed from firm belief that the use of salicylates in the treatment of influenza, chickenpox and some other viral infections is directly a cause of Reye's syndrome to the opinion that salicylates are valuable and virtually innocuous drugs whose use should not be curtailed to any degree.

Most of the participants expressed views intermediate between these extremes and lacking consensus the modal judgment was that some caution was warranted with respect to treatment of children with salicylates and that caution should take the form of professional education and perhaps public announcement of the possible hazard.

Four epidemiologic studies of Reye's syndrome have been done in which the relation of aspirin to the disease could be examined, one each in Arizona and Ohio and two in Michigan.

All of the studies were of the kind referred to as case comparison studies in which one or more comparison subjects are selected for each case and the characteristics of the people in the two groups are compared to learn how they differ.

In this instance, the central point of inquiry was the use of salicylates and other drugs.

In all of the studies the proportion of cases of Reye's syndrome found to have used salicylates prior to their illness was in excess of 95 percent. The proportion of salicylate users among the noncases was much lower than that, ranging generally perhaps to around 50 percent.

All of the studies showed a very strong association between the use of salicylates and occurrence of Reye's syndrome with the risk of the disease estimated at about 10 times higher among children receiving salicylates than among those not so treated.

Some subsequent analyses taking more variables into account have indicated that the risk may be perhaps four or five times.

Several possible explanations may be proposed. All have been mentioned this morning. One, is the association might have arisen by chance.

The statistical analysis indicates this is an unlikely explanation; differences of this magnitude would be expected to occur by chance only one or two times in a thousand trials.

The second explanation is the association is due to bias in the studies. Bias could explain the results if the information collected for each study subject overstated the use of salicylates for Reye's syndrome cases or understated the use for noncases.

Various methods of analysis have shown this was probably not true. For example, the noncases were found to use drugs for fever other than salicylates more frequently than did the cases.

An association such as this could arise if the Reye's syndrome cases had more severe disease than comparison subjects, so the excess proportion of users of salicylates was a result, rather than a cause.

This matter was explored by comparing cases and noncases at equivalent degrees of severity and each classification of Reye's syndrome and salicylates existed.

The third explanation is the association reflects some causal link between salicylate usage and occurrence of Reye's syndrome. The enterprise studies do not prove this to be true. In the absence of information on how the disease is produced is a serious deficiency. However, given the evidence presently available, this is the most probable explanation.

This conclusion does not rule out the likelihood that other factors may be involved for clearly the vast majority of children who take salicylates do not suffer Reye's syndrome.

However, it does require that consideration be given to ways to reduce risk and the most obvious one is reduce the use of salicylates. Salicylates are valuable drugs and to remove them from the market is not feasible, nor desirable, nor even suggested by anyone with whom I have spoken.

Physicians and parents should be made aware of the potential hazard. This is, I think, the minimum acceptable response to the problem.

I believe that salicylates are used much too freely in the treatment of children with modestly elevated temperatures and that a reduction of that use, especially for children with influenza and chickenpox would carry no penalty at all.

Taking action on evidence that is incomplete or inconclusive is commonly required of us and the decision to do so is usually uncomfortable and sometimes agonizing.

However, in this instance, we have sufficient information that salicylates may pose a hazard that to do nothing appears to me to be irresponsible.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Stallones follows:]

STATEMENT: Hearing before the Subcommittee on Natural Resources, Agricultural Research, and Environment of the Committee on Science and Technology, Congress of the United States, 17 September 1982.

Prepared by: Reuel A. Stallones, M.D., M.P.H.
Dean and Professor of Epidemiology
School of Public Health
The University of Texas
Health Science Center at Houston

Mr. Chairman, Members of the Committee:

My name is Reuel Stallones, and I am Dean and Professor of Epidemiology of the University of Texas School of Public Health. I was Co-Chairman, with Dr. Richard Johnson of Johns Hopkins University, of a public meeting on Reye's Syndrome, sponsored by the Food and Drug Administration on 24 May, 1982. The meeting was attended by scientists engaged in research on the association between salicylate usage and Reye's Syndrome, representatives of and consultants to drug manufacturers concerned with the problem, and a group of scientists knowledgeable in these fields of research but not identified with either of the other two classifications. The meeting was arranged for presentation and discussion of research, and was not planned to yield anything resembling a Committee report of findings and conclusions. However, Dr. Johnson and I attempted to summarize the opinions expressed, especially those of the non-affiliated participants.

During the course of the conference, the full array of opinions was expressed, from firm belief that the use of salicylates in the treatment of influenza, varicella, and some other viral infections is directly a cause of Reye syndrome to the opinion that salicylates are valuable and virtually innocuous drugs whose use should not be curtailed to any degree. Most of the participants expressed views intermediate between these extremes, and, lacking consensus, the modal judgement was that some caution was warranted with respect to treatment of children with salicylates, and that caution should take the form of professional education, and, perhaps, public announcement of the possible hazard.

Four epidemiological studies of Reye's Syndrome have been done in which the relation of aspirin to the disease could be examined, one each in Arizona and Ohio and two in Michigan. All of the studies were of the kind referred to as case/comparison studies, in which one or more comparison subjects are selected for each case, and the characteristics of the people in the two groups are compared to learn how they differ. In this instance the central point of inquiry was the use of salicylates and other drugs.

	Salicylate Users/Cases	Salicylate Users/Comparison	
Arizona	7/7	8/16	
Michigan 1	24/25	30/46	Mar/Apr 80
Michigan 11	12/12	13/29	Sep 80-81
Ohio	94/97	110/156	1978-

Thus, all of the studies showed a very strong association between the use of salicylates and the occurrence of Reye's syndrome, with the risk of the disease estimated to be about ten times higher among children receiving salicylates than among children not so treated.

Several possible explanations can be proposed.

1. The association arose by chance. The statistical analyses indicate that this is an unlikely explanation, for differences of this magnitude would be expected to occur by chance only about 1 or 2 times in 1000 trials.

2. The association is due to bias in the studies. Bias could explain the results if the information collected for each study subject overstated the use of salicylates for Reye's syndrome cases or understated the use for non-cases. Various methods of analysis have shown that this was probably

not true; for example the non-cases were found to use drugs for fever other than salicylates more frequently than did the cases. An association such as this could arise if the Reye's syndrome cases had more severe disease than the comparison subjects, so that the excess use of salicylates was a result rather than a cause. This matter was explored by comparing cases and non-cases at equivalent degrees of severity, and in each classification the association of Reye's syndrome and salicylates persisted.

3. The association reflects some causal link between salicylate usage and the occurrence of Reye's syndrome. The epidemiological studies do not prove this to be true, and the absence of information as to how the disease is produced is a serious lack. However, given the evidence presently available, this is the most probable explanation.

This conclusion does not rule out the likelihood that other factors may be involved, for clearly the vast majority of children who take salicylates do not suffer Reye's syndrome. However, it does require that attention be given to ways of reducing the risk, and the most obvious one is to reduce the use of salicylates. Salicylates are valuable drugs and to remove them from the market is neither feasible nor desirable. Physicians and parents should be made aware of the potential hazard; this is, I think, the minimum acceptable response to the problem. I believe that salicylates are used much too freely in the treatment of children with modestly elevated temperatures, and that a reduction of that use especially for children with influenza would carry no penalty. Taking action on evidence that is incomplete or inconclusive is commonly required, and the decision to do so is usually uncomfortable and sometimes agonizing. However, in this instance we have sufficient information that salicylates may pose a hazard that to do nothing appears to me to be irresponsible.

Mr. SCHEUER. Thank you very much, Dr. Stallones. Have you had an opportunity to examine the raw data? The case records?

Dr. STALLONES. No, sir.

Mr. SCHEUER. How do you react to Dr. Hurley's suggestion that no medical professional has seen the raw data and have a credible judgment on cause and effect relationships here?

Dr. STALLONES. I certainly accept the——

Mr. SCHEUER. Dr. Eichenwald, I think, also expressed that view.

Dr. STALLONES. I certainly agree that in the review of a problem the ability to work with the original records is a very useful thing. However, I would——

Mr. SCHEUER. They say it is indispensable.

Dr. STALLONES. With all due respect, I would say that everyone whom I know in the practice of medicine or in science reads papers, reaches conclusions, evaluates information without researching the raw data and indeed that that opportunity is by far the exception, rather than the rule.

I would suggest that virtually everything that physicians do or believe is correct is based on information which was secondary, not primary.

Mr. SCHEUER. But when it is secondary, isn't that when there is a pool of raw data that is or has become proven or tried and tested and accepted the medical profession because it has been open to public scrutiny and because scientists in and out of Government have mulled over it and considered it and given it some imprimatur of scientific validity?

Then all kinds of people can, and scientists, of course, can build on that brick by brick. But, without the underlying foundation of a credible data base that has stood the test of scrutiny of the medical community, I think they feel, and I am concerned too that you don't have a scientifically justifiable reason for building on that data base if the data base itself is not or has not been subject to the scrutiny of the entire medical community and may be fatally flawed.

Dr. STALLONES. I certainly understand the argument, Mr. Chairman. Again, I would suggest that the reanalysis of raw data by persons other than the original investigators is a relatively recent phenomenon. It is not enshrined in medical tradition. However, the mechanism which has been used to confirm findings which are uncertain or controversial has been repetitious replication of the work. It has been said that a finding should not be considered correct until it can be transferred from one laboratory to another.

A good many errors do occur in science and we need to protect ourselves against them as much as possible.

One of the reasons why I believe so many panels of distinguished scientists have looked at this issue and have concluded that there were grounds for concern is that——

Mr. SCHEUER. We all agree there is grounds for concern. There isn't the slightest question about that.

Dr. STALLONES. Grounds to proceed to do something.

Mr. SCHEUER. Grounds to proceed with the labeling. This is the biggest question. Whether the depth and reliability of the data base, of the case history, raw data, has been subject to enough review and scrutiny to give medical professionals a solid feeling of

comfort and security in moving ahead to this order of magnitude of reaction.

It is a question of whether the punishment fits the crime, not whether there is a justification of some very real concerns.

There is no question but there is room for concern here and I sympathize with Secretary Schweiker and the fine scientists working with him at the nest of problems they face here. I sympathize as to how in the real world we react to the evidence that is available and the deep concern expressed.

It is not an easy question. The question we are faced with is should they, the medical community in government and out, go back to the drawingboard a little bit to improve the reliability of the data base on which they are acting before opening up this Pandora's box?

We are never going to be able to close that box and go back to position zero again. The results as we have heard the testimony this morning of going public through the media, through the television tube and the radio and going directly to mothers through the patient package insert, to the warning, is irreversible and it is not subject easily to recasting, redefinition, fine-tuning as further scientific evidence is adduced and analyzed and public policy decisions made.

That is the question here. Not whether there is room for concern.

Let me ask you, Dr. Stallones, do you concur with the FDA working group report?

Dr. STALLONES. I think it is not appropriate to concur or fail to concur with the FDA working group report. I have read it and I have reviewed it in modest detail.

In general, I believe that the FDA working group report is in support of the findings of the researchers in Ohio and Michigan—the FDA working group analysis is in accord with the original analyses which were done.

They found some differences but generally they are in agreement.

Mr. SCHEUER. I have been informed—and I make it clear I am not a scientist, not a doctor; I have not done original research work and I am not prepared to write a scientific monograph—but I have been informed that the FDA working group report found that the Ohio, the first year Ohio report, the Michigan data, the Arizona data could not possibly support a cause and effect relationship between the administering of aspirin to a child and the child's later becoming a victim of Reye's syndrome.

As I am informed on this, the FDA working group found there is no way, absolutely no way of finding a verifiable and probative cause and effect relationship between prior taking of aspirin and suffering Reye's syndrome.

Have I been incorrectly informed?

Dr. STALLONES. I am unaware of a statement that is quite that—or one that is quite of that nature in the report.

I am aware of the May 24 meeting at which the people who did the analysis for FDA were present and I have discussed this matter with them in that meeting and also outside the meeting and it is simple enough to check this out because the FDA staff may be queried with respect to this, but my firm belief is that they believe

that the association between Reye's syndrome and salicylate use is strong.

Mr. SCHEUER. What about the apparent extent of biases like misdiagnosis, product confusion, and the parents not being clear whether the medicine was given before or after the onset of Reye's syndrome?

Dr. STALLONES. I attempted to address some of those issues in the statement just briefly which I have prepared. I am unaware of a world which is free of bias.

We live with bias constantly.

I think in the face of bias in our research we have several responsibilities. One is to attempt to estimate the magnitude and direction of the bias and its effect on our conclusions.

I believe anyone who has looked at this issue would believe that serious bias exists in the studies that are being done.

However, the studies are remarkably consistent. That may be because they incorporate the same kind of bias, of course.

Mr. SCHEUER. Yes.

Dr. STALLONES. Some extraordinarily distinguished groups of people have looked at this and have concluded that it would be wise for parents of children who have influenza and chickenpox at least to use aspirin only if the reduction of fever was an overriding consideration.

Mr. SCHEUER. Our counsel, the distinguished majority committee counsel, Mr. Shacknai.

Mr. SHACKNAI. With respect to the last statement about a number of prestigious groups so concluding, was it not the opinion of the overwhelming majority that this was the case with all medication; that in the case of fever no medication should be used unless the fever is in fact, as you stated it, an overriding consideration and that aspirin was in fact not singled out?

Dr. STALLONES. I believe that stated as a general principle, reduction in medications could be accomplished to the benefit of the world.

However, the group to which I had reference was addressing specifically the issue of salicylate use and Reye's syndrome, the CDC consultant panel.

Mr. SHACKNAI. You started out with several prestigious groups and now we are down to one group. As to that group, I would remind you that in your response—

Dr. STALLONES. If I may, Mr. Shacknai, the Surgeon General's advisory with respect to this cites the CDC consultant panel, the American Academy of Pediatrics Committee on Infectious Diseases which issued a similar statement, and I think somewhat erroneously cites—well, it cites the FDA working group but I think that is a different kind of issue.

There was an NIH consensus development conference and I guess when I said several I meant three.

Mr. SHACKNAI. But in other words the NIH consensus panel did not issue such a statement as described but have issued a statement that physicians ought to be warned about this possibility, but that generally the best course of action is to eliminate or reduce the use of all medications when flu and chickenpox are present unless the fever is an overriding consideration.

So what we are really down to is the CDC working group which, as we have noted earlier, had no access to raw data and at that point in time it is suspect that CDC personnel were given access to raw data. We have correspondence to support that.

As to the AAP, they also had no access to raw data, but were in fact relying upon representations made by officials from the CDC.

It is my further understanding that AAP is now in the process of reanalyzing the data in light of the fact that the raw data has become available through freedom of information suits and may be on the verge of actually changing their view on the matter.

Would you find that persuasive if they did change their view?

Dr. STALLONES. If evidence is presented to indicate that there is no credible link between salicylates and Reye's syndrome, I think all of us should change our minds.

I certainly have changed my mind in the past once or twice.

Mr. SHACKNAI. Sure.

Mr. SCHEUER. Well, we have the advice rolling down to us from past centuries that those who fail to learn the lessons of history will be condemned to repeat them, and that a rigid inconsistency is the hobgoblin of small minds. So we ought to all be open-minded and ready to absorb new knowledge and new information as it comes.

Dr. Stallones, we very much appreciate your very thoughtful testimony. We are grateful to you for coming here. We are grateful for your patience in waiting till the end of this long morning. We thank all the witnesses and we assure you that we will, as soon as the transcript is complete, send it down to the Secretary of Health and Human Services who has this enormously perplexing and complicated job of parceling out all the disparate elements and coming to major policy decisions.

I don't envy him and the enormously difficult decisions he has to make. I do thank all the witnesses for coming and giving us of their experience and their wisdom.

Let me add one word of thanks to our majority counsel, Jonah Shacknai, who has designed and prepared this hearing with such outstanding professionalism and with such meticulous concern.

Thank you.

This hearing is terminated.

[Whereupon, at 12:55 p.m., the subcommittee was adjourned subject to the call of the Chair.]

REYE'S SYNDROME

WEDNESDAY, SEPTEMBER 29, 1982

HOUSE OF REPRESENTATIVES, COMMITTEE ON SCIENCE AND
TECHNOLOGY, SUBCOMMITTEE ON NATURAL RESOURCES,
AGRICULTURE RESEARCH AND ENVIRONMENT,

Washington, D.C.

The subcommittee met, pursuant to recess, at 9:39 a.m., in room 2325, Rayburn House Office Building, Hon. James H. Scheuer (chairman of the subcommittee) presiding.

Present: Representatives Scheuer and Schneider.

Staff present: Jonah Shacknai, counsel to the chairman; Maryanne Bach, minority counsel; Kim Moses, staff assistant.

Mr. SCHEUER. The Subcommittee on Natural Resources, Agriculture Research and Environment will come to order.

Today we are continuing our investigation into the alleged relationship between aspirin and a very rare childhood disease but one that is very serious and sometimes fatal, Reye's syndrome.

The week before last, our subcommittee heard from several medical experts and practitioners and scientists and even from the discoverer of Reye's syndrome in the United States that the evidence that there is some kind of cause and effect between ingesting aspirin and developing Reye's syndrome is far too tentative and far too flawed for any type of regulatory action to be contemplated.

Indeed, they cautioned that the kind of actions then being considered by the Department of Health and Human Services could actually do great injury to the 150,000 juvenile arthritics in our country for whom aspirin is by far the best drug of choice; in fact it is the only drug of choice and far less toxic than the available options.

With the backdrop of these warnings by the top professionals in the field, I was especially concerned when Secretary Schweiker announced last week that the Department of HHS was going ahead with a public education program against aspirin use as well as with labeling changes on aspirin bottles.

The evidence that we heard at our last hearing suggests clearly that the Secretary's announcement, however well intentioned—and nobody questioned the bona fides and the good intentions of the Secretary and Dr. Brandt and the entire department—but the witnesses felt that the action that was based on what they considered very dubious evidence was precipitous, premature, and potentially destructive of the public health, especially threatening to the health of the 150,000 juvenile arthritics for whom aspirin is absolutely, virtually the only drug of choice.

Now, this morning we are going to hear from HHS Assistant Secretary Brandt, who will explain the administration's actions in this

matter; I am sure we will have some questions for Dr. Brandt about his department's position on this matter, and we hope that by the end of the hearing the subcommittee will have a better understanding of the reasons behind Secretary Schweiker's announcement.

We will also hear this morning from Dr. James Orlowski of the Cleveland Clinic Foundation, who, besides being an outstanding pediatric intensive care unit specialist, was a participant in the Ohio study on Reye's syndrome, the study that apparently was crucial to the Department's decision.

Dr. Orlowski presumably will raise some very serious questions about the way the data were handled in that study.

I would now, in the absence of our ranking minority member, ask our first witness, Dr. Brandt, to proceed at his discretion.

Dr. Brandt, we are very happy to have you. Nothing that has happened or will happen here this morning will impugn to the slightest degree your integrity, your essential decency, and your bona fides in this matter. The only thing that will be questioned are the judgmental factors involved in making this decision.

Your full testimony will be printed in full in the record at the conclusion of your oral presentation. You can either chat with us informally, then we will have some questions, or if you prefer, go ahead in any way you wish.

STATEMENT OF EDWARD N. BRANDT, JR., M.D., ASSISTANT SECRETARY FOR HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY HARRY M. MEYER, JR., M.D., DIRECTOR, NATIONAL CENTER FOR DRUGS AND BIOLOGICS, FOOD AND DRUG ADMINISTRATION; WALTER R. DOWDLE, PH. D., DIRECTOR, CENTER FOR INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL; GERALD QUINNAN, M.D., DIRECTOR, DIVISION OF VIROLOGY, NATIONAL CENTER FOR DRUGS AND BIOLOGICS; AND EUGENE HURWITZ, M.D.

Dr. BRANDT. Thank you very much, Mr. Chairman.

Let me first begin by thanking you for the coffee. That was a very nice touch that we certainly appreciate.

I am accompanied this morning, on my left, by Dr. Walter Dowdle, who is director of the Center for Infectious Diseases of the Centers for Disease Control; and on my right, Dr. Harry Meyer, who is director of the National Center for Drugs and Biologics; and Dr. Jerry Quinnan, who is director of the Division of Virology of the National Center for Drugs and Biologics.

I think it also ought to be pointed out, Mr. Chairman, that Dr. Johnson, who was the American discoverer of Reye's syndrome and published the first paper, did so while serving as an epidemic intelligence officer of the Centers for Disease Control, so that the Centers for Disease Control has been involved in Reye's syndrome for some years.

I would like to begin by summarizing my previously submitted statement describing the scientific background and the outline of the Department's recently announced activities to inform the public of what we believe to be the association between the use of

aspirin and other salicylate-containing drugs and the development of Reye's syndrome.

This association is not new. A number of investigators over the past 20 years have suggested that Reye's syndrome may be associated with salicylates. However, it was only when results of recent case-control studies became available that an assessment of a possible association with specific drugs could be made.

As of late 1980, three case-control studies, which included matching for antecedent illness, had been conducted by the Arizona, Ohio, and Michigan State Health Departments. The results of these studies tend to indicate an association between Reye's syndrome and the ingestion of salicylates during the antecedent illness.

On the basis of review of those three studies, CDC published a recommendation in the Morbidity and Mortality Weekly Report on November 7, 1980, and I quote: "Parents should be advised to use caution when administering salicylates to treat children with viral illnesses, particularly chickenpox and influenza-like illnesses."

In November 1981, CDC convened a group of outside consultants to review these State studies. Those consultants concluded, and again I quote, that there is "strong epidemiologic evidence for an association between the occurrence of Reye's syndrome and the prior ingestion of salicylate-containing medication." They further recommended, and I quote, "Until the nature of the association between salicylates and Reye's syndrome is clarified, the use of salicylates should be avoided when possible for children with varicella infections and during presumed influenza outbreaks."

Again, in the Morbidity and Mortality Weekly Report of February 12, 1982, CDC again reported this association and stated that: "until definitive information is available, CDC advises physicians and parents of the possibility of increased risk of Reye's syndrome associated with the use of salicylates for children with chickenpox or influenza-like illness."

In response to the reported association between salicylates and Reye's, the Food and Drug Administration formed a working group composed of members of the agency to review the available data to determine the quality and the strength of the association.

Now, they recognized that the studies required careful evaluation, both because of the inherent limitations of case-control methodology and because of questions raised by earlier reviews of the studies. In evaluating the available data, the working group activity included a number of reviews and actions, all of which are detailed in the prepared statement.

This working group prepared a preliminary report of its review, and that report was dated May 18, 1982. It presents a detailed discussion of the results of the studies and the working group's analysis of the data.

The working group found that cases of Reye's syndrome in the study were significantly more likely to have used salicylates, and this association continued even when the data were statistically adjusted to account for differences in the cases and the controls, for the symptoms of headache, fever, sore throat, and cough, and when cases with four or fewer days between the onset of antecedent illness and the onset of Reye's syndrome were eliminated.

In addition, and of interest, the working group found that there was significantly less use of acetaminophen in the cases than in the controls.

A workshop sponsored by the FDA, the CDC, and the National Institute of Allergy and Infectious Disease of the National Institutes of Health was held on May 24 to discuss the currently available data and to accept written submissions and hear oral presentations.

The invited scientific panel members were asked to review and discuss the data and presentations, but were not asked to make formal recommendations to the sponsoring organizations. The members, however, were provided an opportunity to comment at the close of the meeting, and many of the experts indicated that the available data tend to establish an association between salicylates and Reye's syndrome and that physicians and the public should be advised of that association.

Now, we fully recognize that the available data do not establish a cause-and-effect relationship between salicylates and Reye's syndrome. Indeed, case-control studies such as those which have demonstrated this association are intended to detect associations but not to prove causation.

However, the FDA has examined the studies and analyzed the data critically, attempting to insure that the common distorting elements have not created a false association.

With rare diseases such as Reye's syndrome, we have no option except to rely on case-control studies because prospective studies of a population at risk for a disease that may occur at a rate of fewer than 5 cases per 100,000 population under age 16, not experiencing a flu epidemic would require an enormous number of subjects.

However, it is important to point out that the four studies are consistent in their results, which tends to confirm the validity of the association which each study purports to establish individually.

Collectively, the results of the studies on their face establish a strong association between salicylate ingestion and Reye's syndrome. Moreover, the Ohio and Michigan studies appear to establish a reverse association with the administration of acetaminophen, in that control subjects were much more likely to have received this drug than were the cases.

This reverse association tends to contradict contentions that the studies were compromised by recall bias.

Until the basis for the association can be definitely established, we believe that the interest of the public health requires that physicians and the public be advised of the association and warned against the administration of salicylate-containing medication to children with flu or chickenpox. The American Academy of Pediatrics has also recommended against using aspirin products in such situations.

Over the last several months, we have received additional communication from several sources, including a written report on the analysis of the Ohio Department of Health case-control study of Reye's syndrome performed by the Biometric Research Institute. We have carefully reviewed this information and have concluded that we have not been presented with additional information which would influence our position.

Consequently, on September 20, 1982, Secretary Schweiker announced that we were proceeding with the plan which had previously been announced to propose new labeling requirements for these products. The proposal requires warning labels to alert parents to the risk of using aspirin and other salicylates under certain circumstances.

Specifically, for over-the-counter nonprescription drugs, the warning label would read as follows: "Warning: This product contains salicylate. Do not use in persons under 16 years of age with flu or chickenpox unless directed by your doctor. The use of salicylates to treat these conditions has been reported to be associated with a rare but serious childhood illness called Reye's syndrome."

For prescription drugs, the warning appears in the labeling for physicians and is included herein.

The proposal provides for a 30-day comment period so that interested parties may present their views. We will carefully review any additional information submitted to us during our review of comments on the proposal. The proposed effective date of the final regulation would be 90 days after it is published in the Federal Register—that is, after the final regulation is published in the Federal Register.

The Secretary also outlined plans for a public awareness campaign to alert parents about the possible association between Reye's syndrome and salicylate-containing medications. A key part of the program will be radio public service announcements that will reach parents and physicians before the next flu season.

In addition, this awareness program will enlist the help of consumer and health professional groups to circulate information to the public. Question-and-answer brochures will be sent to physicians and pharmacists which, in addition to providing basic information in language understandable to the lay person, will stress the importance of early recognition of the symptoms of Reye so that hospitalization and supportive therapy can be initiated promptly.

These steps will augment those initiatives which have already been achieved to alert physicians and other health care professionals, namely, the August 1982 FDA Drug Bulletin article and the Surgeon General's advisory which was published in the CDC publication, Morbidity and Mortality Weekly Report, on June 11, 1982.

In conclusion, medical experts have determined that there may be an association between Reye's syndrome and the use of salicylate-containing drug products. We believe that in this instance the risk involved to children of developing a life-threatening illness is of sufficient magnitude that we are obliged to inform the public.

Let me quote in closing, Mr. Chairman, from the testimony presented by Dr. Reuel Stallones, Dean of the University of Texas School of Public Health and one of the country's outstanding epidemiologists, from his testimony that he presented at the hearing on September 17, and I quote: "Taking action on evidence that is incomplete or inconclusive is commonly required, and the decision to do so is usually uncomfortable and sometimes agonizing. However, in this instance we have sufficient information that salicylates may pose a hazard that to do nothing appears to me to be irresponsible."

Thank you very much for this opportunity, Mr. Chairman. We are pleased to answer any questions that you may have.

Mr. SCHEUER. Thank you very much, Mr. Secretary.

Let me ask, when CDC first made its views public in November of 1980, what was the scientific basis for its perception of the relationship between aspirin and Reye's syndrome?

Dr. DOWDLE. That basis, sir, was the results at that time of the three studies, the Michigan study, the Ohio study, and the Arizona study, plus other information which had been presented in the past which also suggested aspirin was involved.

Mr. SCHEUER. Had CDC had the benefit of examining the underlying data in the case report forms prior to that announcement?

Dr. DOWDLE. In the case of all three of those studies, CDC people were involved in the actual working up of the study itself. In Arizona, there was a CDC person that was involved. In Michigan, there was a CDC EIS officer involved. In Ohio, we were working with them in preparing the protocols and also had access to the data.

Mr. SCHEUER. Let me just repeat the question. Did CDC have access to the raw data and the case report forms prior to its announcement of November 1980? Did it have access to the raw data and the case report forms from those three studies?

Dr. DOWDLE. The person at CDC who was working with the State of Ohio had access to that data. We did not have that data at CDC. That was still in Ohio at the time. We did not have a chance to systematically review that data at CDC, no, sir.

Mr. SCHEUER. To what extent did your person, your "man in Havana" so to speak, to what extent did your person in Ohio and Michigan actually study and examine the case report forms and the raw data?

Dr. DOWDLE. He worked with them quite extensively in actually working up the data for presentation.

Mr. SCHEUER. That is not the question that I asked. To what extent did your representative in those three studies have a chance to evaluate and examine the underlying data and the case report forms?

Dr. DOWDLE. The person who was involved in that study is right here, sir. Would you mind if he speaks to that?

Mr. SCHEUER. Of course not.

Dr. DOWDLE. This is Dr. Gene Hurwitz of the Viral Diseases Division at CDC.

Dr. HURWITZ. Let me just first comment on the Michigan study. The Michigan study actually, as Dr. Dowdle has indicated, was conducted by an EIS officer, a CDC person, who was my counterpart in the State Health Department in Michigan, who was working at the State Health Department at the time while I was working in the Viral Diseases Division at CDC.

He was directly responsible for all of the data, for the collection and the analysis of the data at the Michigan State Health Department.

Mr. SCHEUER. What did he have to do with CDC?

Dr. HURWITZ. He was an Epidemic Intelligence Service officer, as was Dr. George Johnson.

Mr. SCHEUER. For CDC?

Dr. HURWITZ. For CDC, that is correct.

Mr. SCHEUER. All right. Let's talk about the Ohio study. That seems to be the key study here. The second year of the Ohio study. Were you involved in the Ohio study?

Dr. HURWITZ. Yes. I was involved in helping to design the protocol and in overseeing the conduct of the study throughout the entire period.

Mr. SCHEUER. Did you have an opportunity, and did you study and examine and review the basic raw data and the case report forms?

Dr. HURWITZ. I did what CDC does under such circumstances when we contract with a State health department or with any investigator to do a study. I went to Ohio several times during the 18-month period of the study, approximately ten times, to review with them, to discuss with them the data. They sent me several interim reports concerning the data. I did review—

Mr. SCHEUER. Excuse me, excuse me. We all have limited time here this morning, and I am trying to get a very specific answer to a very simple question. Did you, as the CDC representative, have access to the raw data and the case report forms, and did you in fact study them?

Dr. HURWITZ. Yes. I did have access and I did study them, certainly not to the extent that, for example, FDA did in their very extensive audit of the data, but I did have access to the case report forms and did spot checks on the various investigations.

Mr. SCHEUER. I don't know what a spot check means. Would you say that you studied the raw data and that you studied the case report forms and evaluated them and analyzed them? You were the CDC's man on the spot.

Dr. HURWITZ. Yes.

Mr. SCHEUER. You were their "man in Havana." Did you satisfy the CDC need to know that the raw data and the case report forms were valid and proper and scientifically sound?

Dr. HURWITZ. Yes, I did satisfy that need for CDC.

Mr. SCHEUER. Did you have access to all the raw data?

Dr. HURWITZ. Yes, I did.

Mr. SCHEUER. You had access to all the case report forms?

Dr. HURWITZ. Yes. Anytime I visited Ohio, I was invited to review any of the records which they had.

Mr. SCHEUER. And did you?

Dr. HURWITZ. Yes.

Mr. SCHEUER. You are satisfied yourself as to the scientific validity and the credibility of both the raw data and the case report forms?

Dr. HURWITZ. To the extent that my role was to review that aspect of the study, I was quite satisfied at the time.

Mr. SCHEUER. Are you less satisfied now?

Dr. HURWITZ. No, I am not; in particular, after hearing the results of the FDA audit, which basically confirmed the fact that this study was conducted quite properly.

Mr. SCHEUER. Our counsel, Jonah Shacknai.

Mr. SHACKNAI. Dr. Hurwitz, I bring your attention to a January 21, 1982, memorandum to Gene W. Matthews, legal advisor to the CDC, to Joel M. Mangle, Acting Assistant General Counsel; subject:

association of aspirin with Reye's syndrome. I quote on the second page, recent developments:

A continuing problem in the review of these findings, the Ohio data, has been a lack of access to the raw data, specifically the individual questionnaires used in the four case-control studies. Because the last three studies are awaiting publication, the State researchers have been reluctant to release sanitized copies of the questionnaires, instead releasing summary data or selected computer printouts.

Is that consistent with what you have just testified to?

Dr. HURWITZ. Yes, it is. I don't think he was referring to CDC's access; he was probably referring to the access of others.

Dr. BRANDT. Right.

Mr. SHACKNAI. Well, again quoting: "The continuing problem in the review of these findings has been, A, lack of access to raw controls." I would then draw your attention, Dr. Hurwitz, to a letter dated March 31, 1982, again well after November 1980, from a Mr. Howe, the contracting and procurements officer at CDC, addressed to Dr. Halpin, the chief investigator. That letter simply requested, for the first time, I gather, that the raw data be released pursuant to the provisions of the contract under which CDC funded the study.

Dr. Ackerman, the chief individual at the Ohio Department of Health, refused such data, claiming it would be an invasion of the Ohio Department of Health's privacy.

I would then refer your attention to a May 25, 1982, letter from Dr. Brandt to Dr. Ackerman, again requesting the data and incanting the contractual provisions under which the Ohio Department of Health was obligated by law to release such data. Is that consistent with what you have just testified to?

Dr. HURWITZ. Yes.

Dr. BRANDT. I think, Mr. Shacknai, that there are two issues involved. One is whether or not the CDC people who were directly concerned with the study had access to that raw data, and Dr. Hurwitz has testified that he indeed did and reviewed them.

The second issue, and the issue about which I wrote my letter to Dr. Ackerman, related to whether or not we could make those data available to our outside consultants. There have been a number of outside consultants who have looked at these data, both for CDC and FDA, and the issue there was whether or not the raw data could be made available to those persons.

Instead, we did have access to a computer tape which included the data but not to the report forms for that purpose. That is not an unusual occurrence when scientists are going to publish material; in fact, the Journal of the American Medical Association specifically has a rule that they will not permit manuscripts to be published when the information has been published elsewhere. The New England Journal and other journals have the same thing. So it is not an unusual occurrence for them to want to do that until their article is published.

Of course, I was not around prior to November 1980, but I think that the letters that you are referring to deal with a separate issue.

Mr. SHACKNAI. Well, just for the record, Dr. Brandt, every piece of correspondence that has fallen into the hands of the subcommittee, including an actual deposition by Thomas Halpin, would indicate that in fact neither members of the CDC team nor members of

any other Federal Government team did in fact have access to the raw data really at any point until the FDA group came in and did its preliminary review, and even then they were not permitted to remove such data from the premises, nor to make photographic reproductions of such data.

Dr. BRANDT. Yes, I am aware that that restriction was put on the FDA. Yes, sir.

Mr. SCHEUER. In regard to the CDC panel, as you indicated, CDC convened a panel of scientists in October of 1981 to review the Ohio, Michigan, and Arizona studies. What was the basis of that? Should I ask Dr. Dowdle?

Dr. BRANDT. Yes, Dr. Dowdle can answer that.

Mr. SCHEUER. What was the basis of that group's report, and had that group seen and examined the raw data and the case report forms?

Dr. DOWDLE. They in fact recommended that caution should be exercised, pretty much what Dr. Brandt referred to earlier. They also said that there should be a review committee convened to look at that, which is the next step that was taken with the FDA.

They did not see the raw data, no, sir. They saw the data presented by the different authors, but they did not see the raw data.

Mr. SCHEUER. Nor the case report forms?

Dr. DOWDLE. Nor the case report forms.

Mr. SCHEUER. All right. Now, some time earlier in 1981, the NIH convened a consensus conference. This is apart from the CDC meeting. What were the results of that conference?

Dr. BRANDT. In the first place, that conference was aimed principally at dealing with the issue of diagnosis and treatment of Reye's syndrome, and no presentations were made concerning these particular studies in a formal fashion. They were discussed.

But the NIH consensus panel did issue a statement indicating caution in the use of medication, specifically salicylates, in children with either chickenpox or influenza, but again, the NIH consensus conference was not aimed specifically at, nor was it called specifically for, the purpose of looking at the etiology of Reye's syndrome but rather diagnosis, management, and so forth.

Mr. SCHEUER. Did they have any more access to information than did the CDC group?

Dr. BRANDT. As a matter of fact, to the best of my knowledge—I don't know what was informally given to them, but to the best of my knowledge, there was no formal presentation of the data from any of the studies, so that, in effect, one could, I think, say honestly that they had less access to the data from these four case-control studies than did CDC or certainly FDA.

Mr. SCHEUER. Yes. Now, on the FDA involvement, were they asked by CDC to join the February 12, 1982, warning against aspirin in the Morbidity and Mortality Weekly Report?

Dr. BRANDT. Yes, sir, they were.

Mr. SCHEUER. Did they accept?

Dr. BRANDT. No, sir. Dr. Meyer is here, and I think he can give you the FDA's reasoning behind that.

Dr. MEYER. Actually, I was not in my present job at that time so I was not involved, but my understanding—Dr. Dowdle would have been present at discussions—I think the feeling was that FDA was

going to be involved in the independent audit. Since a number of questions had been raised that seemed to make it worthwhile to go into a more detailed audit to answer some of those questions, FDA, I think, was reserving comment until it actually completed the audit which was in progress.

I might add, just in talking about the earlier data, one should not lose sight of the fact that whether it is FDA or scientists in general, much of the decisionmaking in science is made without any attempt to ever audit data. Audits of data often come in when substantial questions are raised which make, then, a more important issue of going after the data. But scientists at many, many scientific meetings come to preliminary conclusions or preliminary judgments based upon data which would essentially be summary data.

Mr. SCHEUER. Yes, but where the data are questioned, then an audit becomes very appropriate.

Dr. MEYER. If data are questioned and there appear to be important questions, then it is usually worthwhile to do an audit, which was the reason FDA then entered into the audit.

Mr. SCHEUER. Did the FDA complete its audit?

Dr. MEYER. Yes, the FDA did complete its audit.

Mr. SCHEUER. Did the FDA have access to the second year Ohio report?

Dr. MEYER. Yes, FDA had access to—

Mr. SCHEUER. The raw data?

Dr. MEYER. Yes.

Mr. SCHEUER. And the case-control reports?

Dr. MEYER. Yes.

Mr. SCHEUER. What was the FDA's conclusion after examining those data?

Dr. MEYER. FDA put out a preliminary report which was then supplemented by additions, and we put together a meeting to discuss it—we did not attempt in the report to come to hard conclusions; we attempted in the report to cover all the parameters of the data. In other words, the intent of our report was to analyze the various aspects of the study, the various data, to look at the various questions that had been raised, and to really shed light on that particular thing.

We then brought those data to a public forum. At the public forum, the conclusion was that the various questions that had been raised did not appear to be sufficiently substantial to negate the conclusion that there appeared to be an association between use of salicylates and Reye's syndrome.

Mr. SCHEUER. Didn't the FDA working group conclude that the only data which would show a causal relationship between aspirin and Reye's syndrome were the Ohio second-year data, if they were valid?

Dr. MEYER. Dr. Quinnan, on my right, is actually a member of the working group who analyzed in detail, and I will ask him to comment on that in just a moment. But I would say there is a misconception on many aspects of the study. All four studies in fact contribute data that are useful and influence scientists in thinking that there is an association. The last year of the Ohio data has a particular type of information in it that allows you to look in a

more penetrating way at certain aspects of that association, but in no sense should one discount the data from the other three studies. The other three studies' data are quite valuable.

Dr. QUINNAN, would you like to say anything about the second year of Ohio?

Dr. QUINNAN. I would add first that case-control studies never demonstrate a cause-and-effect relationship, and we did not anticipate nor try to conclude that the second year of the Ohio study could or could not demonstrate a cause-and-effect relationship.

The principal reason for focusing heavily on that one particular part of a study was that it had data entered in such a way that we could examine the use of aspirin in relation to severity of antecedent illness and other factors and do the types of detailed statistical analyses which would allow us to determine whether those other factors accounted for the excess use of aspirin.

Mr. SCHEUER. Well, would they have valid data of this apparent cause-and-effect relationship based on these studies, other than the second year of the Ohio studies? Were those studies sufficiently credible and accurate, standing on their own; could they have been the basis for a conclusion on the cause-and-effect relationship between Reye's syndrome and aspirin use?

Dr. QUINNAN. Again, I think there is some misunderstanding. Epidemiological studies such as this are methods of identifying associations which may indicate a cause-and-effect relationship. They are the same type of study that was performed to identify the association of tampon use with toxic shock syndrome. In subsequent research—

Mr. SCHEUER. Well, now, wait a minute. We have a lot of testimony, and we are going to have some more testimony when Dr. Brandt is finished, as to the very dubious quality of these studies, all of them. What I am saying is, based on your knowledge of the credibility and accuracy of those other studies—of those other studies, other than the second-year Ohio study—would the Department have acted on the basis of those studies in the rather incredible circumstances that surround those studies?

Dr. QUINNAN. Well, I will not try to say that I know what the Department would do under different circumstances. We found no indication that there were sufficient problems with any of the studies to discard any of them as being useful information.

Mr. SCHEUER. Would they have been sufficiently credible to have justified the decision the Department has taken based on those studies alone?

Dr. MEYER. I don't think that is a question we need to answer, sir, because basically, a scientist is always looking for data that are likely to be available. By the time you would have wanted to take an action or might have considered an action on those three studies, you knew the fourth study and the data were going to be shortly available, and so everybody was looking at those data. You knew you would have them in hand, so you knew you would have the results of four studies to deal with.

I would say the thing Dr. Quinnan was trying to stress a moment ago is to again hammer in—you keep using the term "cause-and-effect relationship." No one feels that the data show a cause-and-effect relationship. The people feel, though, no matter how hard we

critically analyze the data, and FDA, you should recognize, in their audit deliberately tried to see if it could destroy that relationship by every statistical analysis it could make; we were unable, in our best effort to destroy that relationship, we were left with a strong association but an association, not a cause-and-effect relationship.

As the Assistant Secretary has stated, an association of this type is a basis for warning people of the possible association.

Dr. BRANDT. Mr. Chairman, let me address both of these questions, because the issue of whether FDA chose to appear with CDC in the MMWR was a decision that I approved, and therefore I was involved. It related to the fact that, by then, we were becoming increasingly convinced, and had become convinced, as a matter of fact, that the profession needed to have further alerting to this association that was clearly appearing.

The question of whether or not some regulatory action would be required then came up, and it was Commissioner Hayes' and my judgment that in fact, since it was likely that the FDA would have to exercise some regulatory activity, since it was possible, at least, it was not a good idea for them to go on record prior to doing their own independent analysis and their own independent look at the issue, stating some association, when they might be asked officially to do that and, of course, were soon asked by me to do so.

With respect to the four studies that are under question, I think nobody would sit here and tell you that those are all ideal studies. Clearly, they all have deficiencies. I have been hanging around epidemiology for a long time, and I have never seen a perfect case-control study except on final examinations given to students in epidemiology. One does not find them in nature, unfortunately.

Mr. SCHEUER. Aren't there differences of imperfection?

Dr. BRANDT. Oh, sure.

Mr. SCHEUER. This is the whole issue that we are trying to get at now. I suppose you could say there are probably flaws in every scientific study.

Dr. BRANDT. Yes.

Mr. SCHEUER. Nothing is 100 percent perfect. But on a scale of 1 to 100, there must be studies in the 80 or 90 range, and then there must be studies in the 10, 20, and 30 range, and it is this degree of imperfection and unreliability that we are trying to get to today.

Dr. BRANDT. Well, I think that in looking at epidemiologic evidence, either in trying to make decisions, practicing physicians making decisions about how to manage patients or in fact, in this instance, making regulatory decisions, the things that you look for are, one, that there be some kind of an association.

Now, it is very clear that a much higher percentage, irrespective of how you attack the data, of the patients with Reye's had taken salicylates than those who did not develop Reye's syndrome. The second is that all of the studies have been consistent. They have all shown that, and that goes clear back to 1962, even prior to the full definition. There have been a number of other studies through the years that have shown that.

The third is that there be a mechanism, and clear mechanisms for the operation of this effect. We in no way believe that aspirin is the sole cause of Reye's syndrome and would not so state. The question that we were faced with is, at what point do you alert the phy-

sicians? Had this been a prescription drug, clearly, we would have dealt principally with the professions.

Mr. SCHEUER. You see, we would have had no question at all if you had gone to the physicians, because physicians can fine tune their approach. They are far more sophisticated and knowledgeable, presumably, than mothers, lovable and caring as mothers may be.

We would have had no question whatsoever if you had put out an advisory to physicians. But when you go beyond the physicians and over the heads of physicians to the mothers of America and you advise them not to use aspirin for a very small group of kids, what we are afraid of, as you undoubtedly know by now, is that, somehow or other in the fuzzy business of communicating, mothers will interpret this warning as a warning that aspirin is bad, aspirin is dangerous, and that if you take aspirin, your child may get Reye's syndrome; when the fact is that for the overwhelming percentage of the kids for whom aspirin is the drug of choice, especially the 150,000 juvenile arthritics in this country, Reye's syndrome is not a danger, is not a problem.

Our concern is that mothers who should be giving their kids aspirin, kids for whom aspirin is really the only appropriate remedy, for whom aspirin is by far the least toxic of the remedies available, our concern is that those mothers will get an inchoate fear that aspirin is bad and leads to all kinds of horrible diseases, and therefore don't give your kid aspirin.

Dr. BRANDT. Yes.

Mr. SCHEUER. That is why we would have had no reservations had you gone to the doctors of America, who can fine tune their approach to parents and deal directly with the parents whose children might be getting aspirin under conditions that might lead to Reye's syndrome, and distinguish them from this other vast group of parents who are giving their children aspirin quite properly as the best drug of choice for them.

That is what this is all about, not that there would have been anything questionable at all had you gone to the doctors of America, but we are concerned that the remedy does not fit the crime and that the relief does not fit the danger, and that there is a very real and present danger of great overkill and unnecessary suffering and perhaps even death of that 150,000-strong constituency of juvenile arthritics in this country, and that is all we are talking about, not the appropriateness of an advisory to the medical profession.

Dr. BRANDT. Believe me, we share the same concern. Let me point out that since I have been here in the year and a half, I have not found any way to communicate even with one other person without it becoming public knowledge. The MMWR published by CDC is sent to physicians and is primarily intended to be for health professionals.

Mr. SCHEUER. Yes, but, Dr. Brandt, you have already announced that you are going to have an education program via radio to parents, discussing with them, or trying to raise their level of consciousness as to the cause-and-effect relationship between ingestion of aspirin and Reye's syndrome.

Dr. BRANDT. Yes.

Mr. SCHEUER. We think that is going to constitute a real danger to the 150,000 juvenile arthritics who should be getting aspirin. That is what we are concerned about, and you have already announced that you are going to have an educational program directed to those parents.

Dr. BRANDT. Yes, but let me historically give you just some of the reasoning. We initially went to the physicians through the MMWR. That, of course, was released to the media. I mean, that got into the media. We then went through the Drug Bulletin. The Surgeon General's advisories are primarily aimed at physicians, although they usually get wide press distribution.

At no time have we tried to tell the public that aspirin was bad. What we have said throughout is that if your child has either chickenpox or a flu-like syndrome, you should not give aspirin without consulting your physician.

Now, I do not find that that is bad advice to tell them to do that. That is advice that is shared in by the American Academy of Pediatrics, which of course is the group of pediatricians, and they released that information to the public before we did. They feel, clearly, strongly about it, and that includes people who treat patients with juvenile rheumatoid arthritis. We believe strongly that the physicians—

Mr. SCHEUER. I understand that that was their infectious diseases committee and that the full membership and the governing body have not acted yet.

Dr. BRANDT. That is possible. I don't know their mechanism for clearance. It certainly was their expert committee that—

Mr. SCHEUER. We talked to the president last night, and that was what he told us.

Dr. BRANDT. Yes. Well, as I say, I don't know their precise clearance process, but that is at least what they have released.

We would urge that the physicians who take care of patients with juvenile rheumatoid arthritis or with other illnesses where aspirin is an effective drug, that they not discontinue aspirin, that they continue to use it within their judgment.

What we are concerned about is the giving out of aspirin to children who have a very mild fever and giving it in quantities to try to bring their temperature down to normal without any physician involvement, and that is because there are other mechanisms for handling that, and we do not see that the risk ought to be that high.

Besides that, most physicians are used to dealing with the issue of competing risks in managing patients, anyway.

Mr. Scheuer. Don't you understand, Dr. Brandt, we are not concerned with physicians.

Dr. BRANDT. I understand.

Mr. Scheuer. We think any physician advisory that you sent out would have been totally justified and eminently acceptable. We know that physicians are capable of coping intelligently with the information that you have to give them and with the concerns that you wish to express to them. Our only question today is whether this health education program on which you seem to be embarked with parents, on a very sophisticated question, will not become very much more fuzzy. The message that you wish to convey to

them we fear will become much more fuzzy and will end up with sort of a stigma being placed on aspirin.

Dr. BRANDT. Yes.

Mr. SCHEUER. Many parents who think they may have heard something that they did not hear will end up receiving a message that aspirin is dangerous; my child might get some horrible disease; and I had better not give my kid aspirin.

Really, this is the only problem we are talking about, not whether an advisory would not have been totally appropriate to physicians.

Dr. BRANDT. We will, of course, be as cautious as humanly possible in being sure that in our educational program does not become fuzzy and is specific. That is why I think that patients who have chronic illnesses such as juvenile rheumatoid arthritis, who are under the care of a physician, will not become an issue, because those physicians can deal with that problem. I have full faith and confidence in their ability to do that.

Again, what we are concerned about is trying to—

Mr. SCHEUER. How about the danger of malpractice suits? I can see physicians being afraid to prescribe aspirin now on the basis that parents who have heard your message and who receive it a little bit more fuzzily than you send it, being perhaps afraid that parents whose kids do get Reye's syndrome or maybe any other serious disease after having had the doctor advise them to give the child aspirin; these doctors themselves may, consciously or unconsciously, retreat from suggesting aspirin as the best possible remedy, even though, for that child in those circumstances, it would be.

Physicians are commonly known to practice defensive medicine, with the threat of malpractice peering into their work, right over their left shoulder, and they have so testified before our subcommittee.

The business of going to parents with an education program is a very murky and treacherous business, and we just have the feeling that the Department ought to proceed with great modesty as to the possibility of educating parents in an area that requires sophisticated analysis of risks and benefits for particular diseases, and we think they should tread very, very cautiously over this mine field.

Let me get on with a couple of specific questions, and then we will finish up.

Dr. BRANDT. All right, sir.

Mr. SCHEUER. How were the members, and I guess I should address this to—well, I am not sure—Dr. Dowdle, perhaps, or Dr. Meyer—this FDA peer review procedure, Dr. Meyer, when the scientific members of the May 24, 1982, workshop were selected, how were they selected? What were the criteria?

Dr. MEYER. What we were trying to do was to bring the FDA audit into a general public forum, so it was a general public forum. We wanted to be sure, at that general public forum, that we had at least a reasonable number of people who were expert and who had addressed the problem, were familiar with the past data, and would have the opportunity then to ask the types of questions that the people who conducted the FDA audit would be in a position to answer that had not been answered before.

So for that we wanted to have representation from members of the group who had reviewed the data so thoroughly for the CDC. We also wanted to give an opportunity for people representing the aspirin groups, the health interest groups, the consumer groups here in Washington, to participate.

Mr. SCHEUER. Excuse me, Doctor. You just testified previously that the members of this peer review group did not have access to the raw data and the case reports.

Dr. MEYER. I don't think I said raw data then, sir. If I did, I misstated. What I was saying was that—

Mr. SCHEUER. Hold on. Let our counsel address that.

Mr. SHACKNAIL. Well, I think the earlier statement by Dr. Dowdle and by Dr. Hurwitz was that, at the time of the CDC workshop, the participants, from whom you drew for expertise at your May 24 workshop, did not have access to the raw data or detailed analysis of such data, but rather, as you have testified, relied on representations of that data by the study investigators and authors themselves.

Dr. MEYER. Right. We are all in agreement on that. What I was trying to explain is, one of the intents, I mean the primary intent, of this meeting was, you had now completed an impartial audit by the FDA. We had put a quite expert group that had had no prior commitment to it, that represented many scientific disciplines within FDA, to analyze the raw data, to do it in every possible statistical way it could be done.

We wanted to bring that group before the public and, in so doing, to also bring them before some of the scientists who had sat with the CDC reviewing and who had not had the opportunity, as you mentioned, to hear that type of analysis. In other words, they could then directly question somebody who had in fact analyzed the raw data. So that was the primary intent.

So for that type of meeting, one wants to have representation from the earlier groups that had been convened and who had looked at the summary data and then come out with their conclusions, so that they could then question the people who had done the audit.

We also wanted, though, people who had not been previously committed. For example, the two cochairmen for the meeting I picked had not in any prior way been involved in the question of aspirin and Reye's. One was a distinguished neurologist/virologist from Hopkins; the other was a distinguished epidemiologist/public health person, dean at the University of Texas.

So we wanted independent analysis by others who would be expert in the field. So it was a blend of that, but along with that, it was an informal public forum in which any other interested party had an opportunity to question the data, to raise issues, or to present data which they thought may share in it.

So it was a general public discussion but with the focus being on the FDA group that had done the audit to answer questions that could be raised about the data and to say at least what the FDA group had found in their various tests of the various types of statistical associations.

Mr. SCHEUER. Wasn't it somewhat unusual, in this peer review procedure, that 7 of the 16 members of the panel had already par-

participated in the CDC review group and had already expressed an opinion on it?

Dr. MEYER. Well, first, I would not necessarily call this a peer review in that sense. It was a public meeting and a public discussion, but as I just explained, Mr. Chairman, it was important to bring in people who had looked at the data originally so that they could then ask questions of the people who had done the audit. In other words, that group had not had the raw data before. You were trying to give them the opportunity to cross-examine and question the people who had done the audit to see if they could in fact challenge the people who had done the audit and their analysis of the the raw data.

Mr. SCHEUER. Well, now, talking about the people who had done the audit, wasn't it unusual that an investigator of the study being investigated and criticized, Dr. Starko, was actually a member of that panel to evaluate and comment on a study in which he had participated as an investigator?

Dr. MEYER. As I just explained, sir, the so-called panel, the participants at the meeting, more than truly a panel, the participants at the meeting were an attempt to put into the room those who had data to present and who could answer. For example, it was essential that Dr. Starko be there so that she could answer questions that could be addressed to her or criticisms about her particular study.

Mr. SCHEUER. Yes, but she was not there just as a witness or as a resource; she was there as a member of that panel. She was there in effect judging work that she had already done that was under very severe criticism.

Dr. MEYER. You recall, sir, the panel was not asked to give a judgment. This was not an advisory committee meeting in any sense. This was a public workshop.

Mr. SCHEUER. Well, then, what was the purpose of that panel?

Dr. MEYER. The purpose of the meeting, as I said, sir, was to put in a public forum, before interested scientists, including those who had previously looked at the data in a critical way, the data from the FDA audit and to allow the people who had done the audit to answer any questions that could be raised to test their analysis of the data.

Mr. SCHEUER. In other words, that group was not designed to come up with any conclusions.

Dr. MEYER. It was not designed to give specific, formal advice to the agency, no, sir.

Mr. SCHEUER. All right, and I take it that neither the FDA nor the CDC could possibly have expected to get a fresh and objective view on these studies when half of the panel had been previously involved in it.

Dr. MEYER. No, sir, I do not think that is a safe conclusion. I think, in a public forum, bear in mind, if you count total numbers, I would imagine there were probably as many people representing the various aspirin foundations and aspirin companies in the room as there were anyone else. They may have outnumbered the other participants in fact. Everyone had a chance to offer his point of view and express his opinions.

Basically, we were trying to put into a public discussion, as I repeat, a critical analysis of the raw data for people to shoot at and ask questions about, and what we basically came up with at the meeting, as we do in almost any give-and-take scientific meeting, was a broad consensus. I think people sitting there would say the same thing we have said: you cannot show a cause and effect, but in spite of the various challenges that can be raised, when you finish the audit and do all the analyses, you are still left with an association that just cannot be thrown away, and that would be the conclusion that I would come to of the meeting.

Mr. SCHEUER. We are not suggesting that the association should be thrown away, although I noticed that Dr. Brandt, almost every time, in his testimony this morning, where the printed record said "a cause-and-effect relationship," he would interject in his spoken words, "tend to establish." He was watering that down, and quite properly so. I congratulate him for this additional measure of prudence and restraint over his written testimony.

So it seems to me that we are far from establishing the kind of credible science-based cause-and-effect relationship that would have justified the order of magnitude of the Department's response. This is what it is all about.

Let me ask you this question. On June 4, the Department announced its intention to go forward with a public warning and education program. At that point in time, did the Department have in its possession, again, the raw data and the case report forms from the second year of the Ohio study? Did it have that within its possession?

Dr. MEYER. The Department in the sense that the working group, the FDA working group, would have analyzed the raw data, we do not need in our possession the data we have carefully analyzed, so the Department would have done that analysis of those raw data it considered essential to answer the questions.

Mr. SCHEUER. And the case report forms.

Dr. MEYER. We would have reviewed the case report forms.

Mr. SCHEUER. I do not believe we have heard yet this morning that the Department did an intensive study of the raw data and the case report forms. What I remember from Dr. Hurwitz is that he said that he had access to some of them. He had access to some of them. But that is a far thing from saying that the Department had made an analysis of the raw data and the case report forms.

Dr. MEYER. Well, the large group of the FDA work group, sir, represents the Department. In any complex audit, you have members of the audit who actually analyze the raw data and are able to then answer questions on those data. One does not normally have a large box of data that one gives to, say, the Assistant Secretary, and says, "Dr. Brandt, would you like to sit and go through these several tons of data?" Rather, Dr. Brandt will have a series of experts who will carefully audit that data and will be in a position to answer questions he asks as a result of the audit.

Mr. SCHEUER. Did somebody in the Department examine and evaluate each of the case report forms?

Dr. MEYER. Jerry, do you want to answer that one?

Mr. SCHEUER. Every single one?

Dr. QUINNAN. Someone in the Department evaluated each of the case report forms from the Ohio study, first and second year, that were matched to a control, and most of the additional case report forms from the Ohio study where matching was not possible, for whatever reason; in addition, the case report forms from the Michigan studies were evaluated.

Mr. SCHEUER. Isn't it true that the FDA working group report was also issued before the critical Ohio case report forms were in the possession of the Department?

Dr. QUINNAN. The FDA working group did their analysis by on-site review and careful tabulations made directly from the original case report forms, and then the further calculations were done back here in Washington.

The FDA made two visits to copy the forms, to make detailed reviews to make sure the copies were absolutely correct and, in that sense, had a direct access to the case report forms for their analysis.

Mr. SCHEUER. Did they look, did they actually review and examine each of the case report forms before making their final decision?

Dr. QUINNAN. Yes, sir.

Mr. SCHEUER. Yes, they did. What were the circumstances surrounding the Department's ultimate acquisition of the Ohio case report forms?

Dr. MEYER. We are again talking about two things. It reminds me of the early part of the conversation. The FDA audit group had total access to all data in the studies that it went out to do the direct audit on. The separate question is what raw data could be separately obtained, let's say to provide the aspirin foundation or other groups, and I think that is the subject, and Dr. Brandt could—

Mr. SCHEUER. No, that is not the question that I asked. There are a lot of questions to be asked. I just asked one of them.

Dr. MEYER. Perhaps I misunderstood.

Mr. SCHEUER. What I asked was, what were the circumstances surrounding the Department's acquisition of the case report forms and the raw data from the second year Ohio studies? That is the question that I asked.

Dr. MEYER. Well, I can speak for FDA. As I say, FDA had access and took from those forms that information it felt it needed in its audit, so that is an answer. Yes, FDA had access to that; FDA reviewed those forms; FDA abstracted from those forms what information it needed to come back to Rockville and to continue its audit and statistical analysis.

Mr. SCHEUER. Isn't it a fact that the State of Ohio, completely apart from its contractual obligations, refused to turn over to the Department the case report forms from the study which the Department funded?

Dr. MEYER. Again, sir, you are mixing two things. That has nothing to do with FDA's audit which you can say was for the Department. What you are addressing is the question of the Department trying to obtain information to distribute to other parties, other than the Department itself.

Mr. SHACKNAI. Dr. Brandt?

Dr. BRANDT. Yes, sir?

Mr. SHACKNAL. Under the terms of the contract with the Ohio Department of Health, as we have read it several times, that department was obligated on request, to give to your department the raw data and other materials relevant to the study that were requested by your department, and we have a detailed record of such requests made by your department.

What were the final circumstances under which the data were turned over to your department? Did they hand them over to you voluntarily?

Dr. BRANDT. We requested that the FDA working group be permitted to examine the raw data, and they agreed to that. They did put certain conditions on it, as you identified earlier.

Mr. SHACKNAL. I read to you, though, a May 25 letter bearing your signature to Dr. Ackerman, the head of the Ohio Health Department, reminding him of his contractual responsibilities to give to you those data; so can one infer that at that time the data were not in the hands of the department?

Dr. BRANDT. That is correct. It was not at that time in the hands of the department in the sense that we had physical possession either of the forms or of copies of the forms, and as far as I know, we don't have that yet, but we have had access to the data, and I cannot tell you the exact date that you went up there.

Mr. SCHEUER. Dr. Brandt, what do you make of the fact that the mortality rate of Reye's syndrome cases in the Ohio study is about 5 percent, whereas the mortality rate nationally is about 20 percent? Does that send up an early warning signal to you?

Dr. BRANDT. Well, except there is one item of information that is not present in that determination. The national mortality rate, which is based upon CDC surveillance of Reye's syndrome, is a voluntary surveillance program and is one where physicians around the country are encouraged to report cases of Reye's syndrome.

We believe that it, like most of our surveillance systems that are voluntary, receives primarily reports of the more serious cases. In Ohio and one other State, Michigan, there is a very intensive surveillance system carried on by the State Health Department, and in both of those States, the mortality rate from Reye's syndrome is significantly less; that is, it is less than 10 percent.

We believe that those surveillance systems which are very actively pursued by those two health departments probably are a better reflection of what the national mortality rate is than is CDC's.

We intend to get more vigorous in our surveillance in the future, so I think the mortality rate in the Ohio study is not terribly different from what Ohio has been experiencing in their own surveillance system for several years.

Mr. SCHEUER. And along that line, then, what conclusions do you draw from the fact, as indicated from the Ohio study, that the incidence of Reye's syndrome is perhaps 8 to 12 times as high in the State of Ohio as the national average? Is that a result of far better reporting?

Dr. BRANDT. I think so, yes.

Mr. SCHEUER. Or is it the result of misdiagnosis, perhaps?

Dr. BRANDT. I suspect that it is much more likely to be a case of reporting. In general, when you go in and begin to intensively look

for illness, you find it, because physicians in a voluntary reporting system tend not to report every particular case.

I think one can look at, for example, the toxic shock picture. One can look at the Legionnaires, various other entities that we have dealt with through the years, and the reporting tends to go up when attention is focused on it.

Mr. SCHEUER. Dr. Brandt, you said in your testimony that the Biometric Research Institute study was not of great assistance to you. Why did they not provide you with additional information that might have influenced you?

Dr. BRANDT. Well, I think they did not provide us with sufficiently new information. I think most of the things that they considered and pointed out, we had already at one point in time considered or looked at in an attempt to try to test our own strength in this whole issue.

Mr. SCHEUER. Did you at any time before coming to your decision and announcing it, did you ever consult with any of the lay groups involved with Reye's syndrome?

Dr. BRANDT. I did not personally consult—

Mr. SCHEUER. No, I mean did the Department?

Dr. BRANDT. I cannot tell you for sure, but perhaps one of these gentleman can.

Dr. MEYER. The consultation taking place for the public workshop that we mentioned was that we invited representatives from the various Reye's syndrome groups to attend, and although I don't have a list, at least some representatives from the various Reye's syndrome foundations or groups did attend that workshop. In fact, I believe at least one of them made a public statement, did they not, Jerry?

Dr. QUINNAN. Yes.

Dr. MEYER. Yes.

Mr. SCHEUER. We did receive testimony from Paul Hinson of the American Reye's Syndrome Association to the effect that neither he nor any of the other lay associations, the National Association as well as the American Association, neither of them were consulted by the administration before issuing their order. I think there was some feeling—

Dr. MEYER. That would be correct in terms of formal consultation, sir. But what I am saying, at the public workshop where the data were discussed on the FDA audit, they were invited and did participate in that workshop and did have the opportunity to offer any opinions they chose to offer, along with other interested parties, such as the aspirin foundations, the health research groups, and others.

Mr. SCHEUER. Well, it may be that they did have that opportunity, thrown in with a large number of other groups, but they did testify here the week before last that neither of the two major lay associations were ever consulted, and I can only deduce from that that they felt that it would have been appropriate to consult those two groups because they were groups that were exclusively and deeply and intensively interested in Reye's syndrome and that the Department never consulted them in this whole process.

Dr. MEYER. I would just say one other thing, sir. What is coming out is a proposal, and a proposal gives all groups the opportunity

for comment, and certainly we would give serious thought and concern and interest to any comments that are made by various foundations during that proposed period.

Mr. SCHEUER. Yes. I think they felt, I think it was implicit in their testimony that they would have preferred to have been consulted early on in the process of your decisionmaking. I think they feel, to put it succinctly, they would like to be in on the takeoff, not on the crash landing.

Let me just ask, if information were brought to your Department's attention which suggested serious problems with the integrity of the second year Ohio study, would this give you cause for concern and perhaps pause and perhaps to reconsider your decision?

Dr. BRANDT. I think there is no question that were we to discover additional information or discover, or have brought to our attention, other things that we have not considered or that have not been brought to our attention, we would certainly reconsider.

One of the reasons for sending this out as an NPRM rather than as an interim final rule was in fact to encourage that sort of activity. Furthermore, the June announcement, press release by the Secretary, certainly stimulated a lot of opportunity. We were hopeful that our previous—and we did receive from our previous publications in the Drug Bulletin and others information from practitioners and other scientific groups about this issue.

So I do not think there is any question that if we were provided with information that in some way caused us to change our opinion, we would do so.

Dr. MEYER. Can I just make a comment, sir, on that?

Mr. SCHEUER. Sure.

Dr. MEYER. We have been in a posture of continuing to evaluate any questions or comments on the data which have come in right along. For example, the comments that were made about the analysis that was provided to us had been sponsored by the aspirin foundation; that analysis drew several possible conclusions. As we evaluated that, looked at the statistics, we had some real problems. We felt that, No. 1, there were no new data, but, No. 2, some of the statistical things they had done were not fair statistical analyses.

And so we have continued to analyze anything that comes in. I think, since we will not be testifying after Dr. Orlowski, perhaps Dr. Quinnan should comment, because one of the comments that came in had to do with a concern which I think he may have mentioned to someone, which was brought in to us and which we carefully addressed in looking at the data.

Dr. Quinnan, why don't you comment on that?

Mr. SCHEUER. Dr. Meyer, if you wish to stay—Dr. Orlowski will be testifying in another few minutes when we are finished here—if you wish to stay and listen to his testimony, we would be perfectly happy to have you make any comments you wish to make when he has concluded.

Dr. MEYER. I will just make the comment now, sir, that we analyzed at least the concerns that were expressed from him earlier, and we found that those concerns appear to be groundless. He may address other concerns that have not been addressed to us to date.

Mr. SCHEUER. Well, maybe one of you would wish to stay and make any comments you wish after he testifies.

We have been joined by our very involved and hardworking member, Congresswoman Claudine Schneider of Rhode Island. Do you have any questions?

Mrs. SCHNEIDER. Not at this time.

Mr. SCHEUER. No questions at this time.

Our counsel, Jonah Shacknai.

Mr. SHACKNAI. Dr. Brandt, there have been a number of questions raised on the question of confusion by parents as to what medication was administered to the children involved in the study. Are you aware of any measures that were taken in the Ohio study to verify what types of medication were used in an individual case?

Dr. BRANDT. As far as I know, the only measures that were taken were historical; that is, the parents were questioned as to what medications they had given their child.

Mr. SHACKNAI. In other words, there were no built-in verification devices or schemata?

Dr. BRANDT. That is correct. Well, wait a minute. Jerry?

Dr. QUINNAN. There were a couple of different methods of verification that were used to a greater or lesser extent, to whatever extent was possible. First of all, whenever it was possible to view the actual bottles of medication, an effort was made to do that. That was done quite extensively on the home visits, and all of the parents of children with Reye's syndrome were asked to bring bottles in to the hospital.

The second is that products were consistently identified by brand name, which allows you to not simply take the parents' word for it or your own impression of what might be in a particular combination but to verify that.

Mr. SHACKNAI. Isn't it possible, though, that within a particular brand such as Congespirin or the Coricidin line, some of the products would contain salicylates and others would, say, contain acetaminophen or some other active ingredient?

Dr. QUINNAN. There are a few products where the same specific name is applied to products containing one or the other. In most cases, the product name differs at least a little. For example, Dristan and Dristan-AF have different antipyretics but different names.

Mr. SHACKNAI. So that might tend to sort of blur things?

Dr. QUINNAN. It could if that was a major point of confusion, but in most respects it was not. For example, one of the drugs, and right now I don't recall—I think it was Congespirin—as a liquid is acetaminophen and as a tablet contains aspirin.

Mr. SHACKNAI. I am reading you now the sworn statement of Dr. Thomas Halpin, chief investigator in the study. He was asked, "Was there any verification procedure or process by which you knew with a reasonable amount of certainty that they did in fact follow any verification procedures?" Answer, "No." "Have you ever made an investigation study since all the raw data were collected to determine whether or not in fact a given patient reported on a questionnaire did take a medication which was in fact verified by looking at the bottle?" Answer, "No."

So, according to Dr. Halpin, the only information that was relied upon in the study was the interviews with involved parents.

Dr. QUINNAN. Perhaps I have given a misimpression. The protocol included viewing the bottles whenever possible. The interviewers were instructed to do so. We don't have any data to tell us precisely how often they were able to do that.

Mr. SHACKNAI. Now, do you have in your possession the protocol for the Ohio study, the one-page flow chart?

Dr. BRANDT. I don't have it right with me.

Mr. SHACKNAI. I presume that someone at the table is familiar with this document?

Dr. MEYER. Dr. Hurwitz may wish to comment on that.

Dr. HURWITZ. I would just like to comment about Dr. Halpin's response. As Dr. Quinnan has indicated, there was an effort in that study—I don't know what he was referring to, but there was an effort in that study; interviewers were asked to obtain brand names, and in fact in over 90 percent of both cases and controls, a brand name was documented on the chart for that particular study.

Mr. SHACKNAI. But that is inconsistent, seemingly, with Dr. Halpin's statement.

Dr. HURWITZ. Yes. I cannot explain what he is responding to.

Mr. SHACKNAI. He was the chief investigator in this study? Dr. Halpin?

Dr. HURWITZ. Yes.

Mr. SHACKNAI. Now, this protocol for the Ohio study, is this the protocol that one would normally expect, as a scientist, to accompany a study of this complexity?

Dr. HURWITZ. There are several documents. This is one of the documents which would be part of what would be considered the protocol for the Ohio study. This particular document describes the method of identifying the cases and the period of time in which there were efforts to do the various procedures in the study itself.

Mr. SHACKNAI. Again, Dr. Halpin was asked if this was the only protocol. He answered yes. He was then asked, "Was there any particular reason why just the flow chart, the document you have in front of you, was used as opposed to a detailed instruction type protocol?" Answer, "We felt this was detailed enough." Would that comport with your view as a scientist, that for a study of this complexity with these issues, with the potential for confusion, that this protocol would be adequate to instruct investigators, people in the field, as to their needs and goals in complying with the study?

Dr. HURWITZ. This does not constitute the entire protocol for the study. The study was originally designed to look at the relationship between certain viral illnesses and Reye's syndrome. The medication questions and the medication issue were later added to the study in an effort to focus on that particular issue, and it was modified at various times.

This and other documents and the methods which have been described in the paper which is now published do constitute what would be considered to be a scientifically acceptable protocol. I think that if that were not the case, it would be unlikely that the paper would be published in the Journal of the American Medical Association.

Mr. SHACKNAL. Now, in your view, dealing with Reye's syndrome as you do at the Centers for Disease Control and within the Department, are there other diseases which are known to mimic or in some way mirror the symptoms of Reye's syndrome? In other words, is this a difficult disease to diagnose, absent a biopsy or some other serological testing?

Dr. HURWITZ. Yes. It can be a difficult disease to diagnose, certainly. There is no definitive diagnostic test for Reye's syndrome. Certainly other diseases must be ruled out, in certain instances, before Reye's syndrome can be diagnosed.

Mr. SHACKNAL. When Dr. Halpin was asked that identical question, the chief investigator of this study, he responded that to the best of his knowledge, it is unlikely that any other diseases could appear to have the same symptoms as Reye's. That is also interesting.

Dr. HURWITZ. I can only comment that I am a pediatrician who is accustomed to taking care of children in the past.

Mr. SHACKNAL. And he is the chief investigator of the study upon which you rely.

Dr. HURWITZ. The decisions concerning the diagnosis of cases of Reye's syndrome were made at the six major pediatric centers within the State of Ohio, all of which have very excellent reputations. The physicians who were responsible for diagnosing those patients and documenting the cases of Reye's syndrome are nationally known, some of them are nationally known for their involvement in Reye's syndrome.

Mr. SHACKNAL. There is no question about that; yet not all of the cases that were reported to the Ohio Department of Health were included in the studies, cases that were reported as Reye's cases. So, seemingly, there would have been some selection criteria implemented by the Department of Health in Ohio, the same Department of Health that, according to this sworn deposition, believes that Reye's is a unique disease in terms of its symptoms, directly contrary to what you have just testified to.

Dr. BRANDT. There is a good reason. I mean, a lot has been made of the fact that some cases were not included. Remember that in the protocol it clearly states that, A, the zero-stage cases were not; and, second, no cases were included that could not be matched, and therefore you would not anticipate having a complete census, and that is classic.

Mr. SHACKNAL. Sure, there is no question about that, but there would have been some editorial decision or scientific decision made in the Department of Health in Ohio.

Dr. MEYER. I think CDC can confirm that, but as the FDA audit looked at it, the criteria which are used— I mean, no criteria for diagnosis are perfect. No doubt there are a few cases in there that are not Reye's. But the best criteria you can have are nationally accepted criteria for what is and what is not an acceptable case of Reye's syndrome, and the criteria which were used in these studies were the criteria essentially developed by CDC and NIH. They are national criteria, and that would be the criteria followed.

The investigator has no basis for altering cases based upon his own interpretation. He has a set of criteria which he is following, but there are a number of reasons for exclusion, and Dr. Quinnan

can speak to that. You were excluding not only based upon—they had to fall within a certain age group; you could not take stage zero, which was the most questionable stage; you could not take patients that could not be matched, for example, if you could not match a chickenpox case, and in fact—Dr. Quinnan, why don't you comment on the example.

Dr. QUINNAN. We reviewed the cases that were and were not matched to make sure or to ask the question, is there any indication that there was a selection bias based on this type of editorial decision, and among the unmatched cases, there were a certain number that were stage zero and, by the protocol, were automatically excluded.

There were an additional number that were preschool, and since the matching process called for matching to classmates, they could not be matched and were automatically excluded.

The remaining patients who were not matched, there were 32. Ninety-three percent of those patients used salicylates. That is very precisely comparable to the 94 of 97, which I think comes out to 94 percent, from the 2 years of the study.

Specifically relating to Dr. Orlowski's patients, he reported 11 that we had records on. Of those, six were matched and five were unmatched for the reasons that I gave you before: Two were stage zero, one was preschool, and two they were not able to match to a control with a similar illness. Of the six that were matched, four out of the six used aspirin. Those were two out of the total of three matched cases from the whole 2 years of the study who did not use aspirin. There was only one nonaspirin user that Dr. Orlowski apparently reported to Dr. Halpin that was not matched in the study, and it was for what appears to be a valid reason according to the study protocol criteria.

Mr. SHACKNAIL. Now, Dr. Quinnan, you have done a detailed analysis of the study. How many cases that were purported to be Reye's by the investigators would have had to have been misdiagnosed, in fact not been Reye's, for the study results to be statistically insignificant?

Dr. QUINNAN. It is an unanswerable question in one sense because of the methods that I used for case-control statistical analysis. You would have to go through each case and find out what happened if you dropped that case or if you misdiagnosed that case, and then do a very long, detailed statistical analysis in that fashion.

Mr. SHACKNAIL. Well, Dr. Meyer just testified a moment ago that probably a few of the cases were not Reye's, which is not an unreasonable view. It is consistent with testimony we have received previously at the subcommittee. Would that tend to cloud the results of this study?

Dr. QUINNAN. Probably not. In general, what happens because of misdiagnosis or some similar type of problem in a case-control study is that any association that might have been detected, were everything exactly right, is likely to be diluted out.

Now, it is conceivable that some other condition related to aspirin use would be also existent here, but even if you excluded patients who used aspirin, who had some other problem, you are still left with almost 100 percent of the Reye's syndrome cases having

used aspirin. So it does not seem that there is any likely way that misdiagnosis could influence the association that was demonstrated.

Mr. SHACKNAI. I have no further questions, Mr. Chairman. Thank you.

Dr. BRANDT. Let me comment on that in part because, again, some people have said that if three patients were misdiagnosed, it would change the statistical significance, and I think the issue comes up—I am a statistician—the issue comes up about what is statistical significance, and traditionally, we use the 5-percent level, but I would like to point out that in doing a number of various kinds of looks at where things ought to be, one cannot hold rigidly to that kind of criteria.

Now, we are talking about—I mean, with a rare disease, if one waits until you get that kind of information, you may very well wait too long, and I personally feel that that is why we have carefully talked about an association and we have talked about statistical significance and that kind of thing, because I think that becomes kind of a red herring, quite frankly.

I would like to comment, Mr. Chairman, on your comments about me “watering down” my testimony, and I would like to say that the general counsel of the Department got hold of it last night and gave me some advice, which I followed.

Mr. SCHEUER. The Ohio case study, had they ever done a case study before?

Dr. HURWITZ. I am certain that they have done various studies of epidemics in their State. I don't know if they have ever done a study of this nature. Certainly CDC has done such a study before, and we provided a great deal of the input and expertise concerning the design and the conduct of this study.

Mr. SCHEUER. Dr. Halpin, who was chief investigator, testified that he had not. The further questions that are raised from that are obvious.

Do you have any questions, Mrs. Schneider?

Mrs. SCHNEIDER. Just a brief question. I wonder if one of you might be able to elaborate a bit on the connection or assumed theoretical connection between certain insecticides and Reye's syndrome.

Dr. QUINNAN. There was a hypothesis advanced a couple of years ago that apparent increased incidence of Reye's syndrome nearby forest areas in Canada might be related to insecticide use. To my knowledge, that has not been confirmed in any way beyond that original hypothesis.

Dr. DOWDLE. There is a report which you may want to hear. Gene?

Dr. HURWITZ. That hypothesis was initially based on some epidemiologic evidence that does not seem to be very strong. More recent data is based upon laboratory studies in mice which suggests that they may have a Reye's-like syndrome as a result of insecticides. These are studies which have been conducted by Dr. John Crocker in Halifax, Nova Scotia, Canada.

I think the general feeling about those studies in the scientific community in which you read about them in the literature is that

there is not sufficient strong evidence, either epidemiologic or laboratory, to implicate such toxins in Reye's syndrome.

There has been a recent task force in Canada, of which I was a member, which attempted to look at this issue and to find evidence for an association, and on the basis of their review and an independent epidemiologic study which was attempted, we have been unable to find any evidence for an association between the toxins in the province and Reye's syndrome.

Mr. SCHEUER. Just let me interject the thought that there are those who would suggest the same thing about the cause-and-effect relationship between aspirin and Reye's syndrome, and it all goes to underline the need, in this extraordinarily difficult area, for all parties concerned to tread very carefully in, as I said before, what is proving to be a minefield.

My distinguished colleague, Mrs. Schneider.

Mrs. SCHNEIDER. Just to follow up on that line of questioning, I was wondering if there was any kind of monitoring program, for example field studies, being done. I think the association that has been referred to is in the insecticide spraying of the spruce budworm, and I was wondering if we are doing any monitoring in the United States where we are doing spraying for that purpose.

Dr. HURWITZ. There is surveillance, for example, going on in the State of Michigan. I am not certain that they use the identical spray. There are various States which do spraying programs.

Whenever there are clusters or outbreaks which are reported, we certainly investigate them. We have no reason to believe at this time that there is an association, although we continue to explore that possibility.

Mrs. SCHNEIDER. In what way?

Dr. HURWITZ. By conducting surveillance and consulting with various States where there might be spray programs. As a matter of fact, there was at one time a suggestion of an association between another toxin, aflatoxin, which is not a spray but is something that is produced in various crops which is a byproduct and is found in certain food products.

CDC, in an effort to look at that association, because there was somewhat stronger evidence for an association between aflatoxin and Reye's syndrome, conducted a case-control study several years ago and was unable to find evidence for an association.

Mrs. SCHNEIDER. While I have you here, let me ask you something that is totally off the subject. Are you familiar with the insecticide that is primarily used in the spraying of gypsy moths?

Dr. HURWITZ. No, I am not.

Mrs. SCHNEIDER. No. All right, thank you. That is all, Mr. Chairman.

Mr. SCHEUER. Thank you.

Thank you very much. You have all been very patient and forbearing, and we appreciate your coming up.

Dr. BRANDT. Thank you very much, and let me assure you, Mr. Chairman, that we do intend to walk cautiously through that minefield. As one who has been standing in it for a while, I can assure you that we will be as careful as we can be.

Mr. SCHEUER. What we want you to do is stand instead of walk.

Dr. BRANDT. I am afraid that, unfortunately, we have to get out of it.

Mr. SCHEUER. All right. We understand that, ultimately, a time comes for some kind of forward motion, but perhaps there is maybe a crawl between a stand and a walk that would be the appropriate mode.

Anyway, we are going to hear from Dr. Orlowski now, and you might want to have one of you remain. As I said, we would be happy to hear any remarks that they may care to make when Dr. Orlowski is finished.

Thank you very much.

Dr. BRANDT. Thank you, sir.

Mr. SCHEUER. Now we will hear from Dr. James P. Orlowski, assistant director of pediatrics in the intensive care unit of Cleveland Clinic Foundation in Cleveland, Ohio.

STATEMENT OF DR. JAMES P. ORLOWSKI, ASSISTANT DIRECTOR OF PEDIATRICS INTENSIVE CARE UNIT, CLEVELAND CLINIC FOUNDATION

Dr. ORLOWSKI. Mr. Chairman, Mrs. Schneider, other members of the subcommittee, I am a pediatrician—

Mr. SCHEUER. Dr. Orlowski, do you have prepared testimony?

Dr. ORLOWSKI. I have an outline.

Mr. SCHEUER. All right. I would say that your prepared testimony will be printed in this form in the record, but perhaps if you have an outline you might just as well continue.

Dr. ORLOWSKI. Thank you, sir.

Mr. SCHEUER. Take such time as you may need.

Dr. ORLOWSKI. I am a pediatric intensivist, a physician who specializes in caring for critically ill infants and children. Pediatric intensivists consider Reye's syndrome to be the epitome of pediatric intensive case in terms of a disease in which the child is frequently critically ill, a disease in which, by rapid and proper intervention on the part of a pediatric intensivist, including such things as putting catheters into the brain and the heart of the child, we can frequently prevent significant morbidity or mortality in these children.

Most pediatric intensivists are very familiar with the disease, and in most institutions which have pediatric intensivists, it is the pediatric intensivist who is responsible for caring for children with Reye's syndrome, frequently as a team, such as we do at the Cleveland Clinic.

I have personally cared for approximately 20 children with severe Reye's syndrome and have written four articles on the subject. I also personally worked with Dr. Douglas Reye, the original describer of the disease, who was in Sydney, Australia, at the Royal Alexander Hospital for Sick Children.

I first became concerned after hearing some discussion by some of the individuals who were involved in making some of the recommendations to the American Academy of Pediatrics and the Centers for Disease Control in terms of their expert panel which I first heard about some of the results of the Ohio Department of Health study on Reye's syndrome.

Subsequently, when the August issue of the Journal of the American Medical Association came out and I could actually see the data presented in a format which was beyond question as to what went on in the study, I became concerned because I had personally presented to the Ohio Department of Health, between the times listed in the study period of December 1978 through March 1980, five cases of unquestionable Reye's syndrome in advanced stages which fit the criteria that were listed in the study.

Of the five cases which I reported to the Ohio Department of Health, two cases had absolutely no history of ingestion of aspirin or salicylate-containing products. Yet when I read the study results, I read that 94 out of 97 patients in the entire study, through 2 years, had a history of taking aspirin, which struck me as a little strange that out of the three cases that had no history of ingesting aspirin, two of them could have potentially come from the Cleveland Clinic. That seemed a bit distorted.

Likewise, in the second part of the study, the abbreviated study, the second year study, it was stated that fully every one of the cases had ingested aspirin; 63 out of 63 cases reported during the second period of study in 1980 had ingested aspirin, and yet during that period of time I had reported one case to the Ohio Department of Health who clearly had not taken aspirin.

Not only that, but we also measured salicylate levels in all but one of the cases which we reported to the Ohio Department of Health and had autopsy confirmation on one of those cases.

This to me raised the question of a possible selection bias, because it became obvious to me that the cases that I had reported to the Ohio Department of Health, either some or all of which had been excluded from the study, and I could not quite determine why.

The point has been made by some of the previous testimony that there were reasons for excluding stage zero Reye's syndrome. Clearly, none of my cases that I reported were stage zero Reye's. In fact, I have serious questions about whether stage zero is really Reye's, as do a number of other investigators in the area.

Second, the other reasons for excluding an individual from the study would have been inability to get a control, and yet anyone who works in epidemiology would know that, with perseverance, it should not be that difficult to get controls, especially during the school year when the vast majority of their cases occurred, as they reported in the article.

It became obvious from reading through the protocol of the study that many times what it was was that the line was busy; they only had picked out two individuals as controls, that they could not reach either one of the individuals, apparently on only a few tries; then that case was thrown out.

This raises questions about the selection bias and about the cases that were excluded and as to whether they really were similar. We are told that the cases that were excluded were similar to the cases that were included, and yet if I must assume that my cases were excluded, then it still does not fit, because, clearly, in the second year of the study, it was not 100 percent of the excluded cases that had taken aspirin, because I have at least one case that had no history of aspirin ingestion during that time.

There have been a number of problems with the Ohio Department of Health study in general that have been expressed by others, but I would just like to reemphasize some of the aspects that concerned me.

First of all, the study was retrospective, and although that is an interesting way to identify a problem for further research and further study, it is not the ideal situation on which to make serious recommendations.

There are also problems with retrospective studies in terms of the ability of parents to recall what the medicines were that either the patient took or the control.

In my experience in the intensive care unit, there are frequently errors made in descriptions by parents or names of drugs given by parents in terms of the medications their children were taking and what we actually find on analysis of blood or urine specimens for drugs. This is especially true, for example, in poisoning cases, and most physicians who practice in emergency rooms will tell you that unless they can see the bottle, frequently there is a very big margin of error in terms of what a parent thinks the child took and what the child actually took.

Likewise, when a parent is under the severe stress of having a critically ill child, their ability to remember what they gave that child 7 or 14 days previously, the fact that they can easily be led into stating that, yes, my child took a particular drug, in terms of the line of questioning that the interviewer asks, is a very big possibility.

Likewise, the controls, who were frequently 7 to 10 days out from the episode of a mild illness in their child, would have difficulty remembering accurately what the particular drugs were that they gave the child during illness.

Obviously, the time interval between the illness of either the control or the victim of Reye's syndrome and the time at which the interview is done can severely compromise the ability of the individual to recall the medicines that were taken.

Likewise, I am very concerned about the low death rate that was reported in the Ohio Department of Health study, where they said that there was a 5 percent mortality or fatality rate in their study, and yet, as has already been correctly pointed out, the national statistics show 20 to 40 percent, and in fact, in many of the best institutions in this country in terms of pediatric intensive care units who take care of these critically ill children, we still have mortalities of 20 to 30 percent.

Now, this is a significant improvement over what was going on just a decade to a decade and a half ago, because when Reye originally reported Reye's syndrome, the fatality or mortality was 100 percent. In the late 1960's and early 1970's in this country, the mortality rate was still 70 to 80 percent, and it is only because of the prompt action of pediatric intensive care units, with very sophisticated monitoring and a very aggressive approach to these children, that we have been able to reduce the mortality to what we now consider a significant improvement, down to the 20 to 30 percent range. But a 5 percent mortality is different than I know of in any pediatric intensive care unit in this country, even the best.

Likewise, there is a significant problem with diagnosing Reye's syndrome. I have appended a table to my outline, which I will not go through, a large number of diseases that can mimic Reye's syndrome both in terms of their clinical presentation and, in some cases, even in terms of their pathology, either the liver biopsy or autopsy findings.

Mr. SCHEUER. Which would they be?

Dr. ORLOWSKI. I can spell them out quickly, although most of them you will not be familiar with. Various urea cycle defects; systemic carnitine deficiency, which has a very similar pathology; hereditary fructose intolerance; adipic aciduria, which was reported by the same group in Australia where Reye originally described Reye's syndrome, stating that it has an identical clinical presentation and an extremely similar pathologic presentation; autoimmune hemolytic anemia, which I, myself, reported. Salicylates themselves can present a syndrome that is clinically similar to Reye's syndrome both in terms of the clinical presentation and in terms of the autopsy or biopsy findings. Valproic acid, which is a seizure medicine, has a very similar clinical presentation in terms of toxicity and autopsy or pathology findings. Acetaminophen poisoning can have a very similar presentation, both clinically and in terms of pathology findings.

Aflatoxin, as we have already heard about, tetracycline, methyl bromide poisoning; and then various infections can mimic it, such as sepsis, meningitis, encephalitis, hepatitis, pancreatitis, and, in children under a year of age, sudden infant death syndrome can even mimic Reye's syndrome.

Another problem with the study besides the lack of biopsy confirmation—well, let me address that just once more. I think that most of us manage Reye's syndrome in terms of intensive care chiefly on the basis of clinical presentation and do not require a biopsy to make the diagnosis in terms of the treatment unless it is an unusual case or our treatment does not seem to be working. But we usually initially treat without a liver biopsy.

But when one is going to make recommendations of the magnitude that is being recommended in this article in terms of the association, then it becomes critically important to prove that the cases that you were indeed identifying as Reye's syndrome were Reye's syndrome. In fact, one of the participants in this study is one of the biggest voices in the country for doing biopsies on all children with Reye's syndrome, and that is Dr. Parton, who did reside at Cincinnati but has since changed his affiliation, and he was one of the most vocal individuals for saying that all children should be biopsied who are suspected of having Reye's syndrome and in fact has accumulated much of the data which now shows that, even in early stages, there is at least a 25-percent error in the diagnosis of Reye's syndrome when one uses biopsy confirmation of the data.

Another problem with the study was the lack of confirmation of the medicines. Samples of the medicines were not analyzed. Blood levels in the vast majority of cases were not determined. In fact, we presented blood levels in the cases that we reported, which also shows that we were not totally unaware of what they were looking at, so we were not blind, and I do not believe the investigators and

the nurse practitioners who were doing the interviews were necessarily blind to what was being looked for.

Likewise, a large percentage of the Reye's syndrome cases were excluded, as has already been stated, but the importance is that it is nearly 60 percent of the cases of Reye's syndrome reported to the Ohio Department of Health that were excluded. I wrote to Dr. Halpin and I requested information. I gave him the actual names and the clinical data and our hospital numbers from the Cleveland Clinic of the particular patients that we had reported to him and asked him to comment on why they were excluded, because we were led to believe, obviously, from the inconsistencies between his report in the literature and what we had submitted to him, that our cases had to have been excluded for some reason or another.

After he failed to get back to me in what I considered to be a reasonable period of time, I went ahead and submitted to the Journal of the American Medical Association a letter to the editor expressing my concerns and asking them to get a comment from Dr. Halpin as to why my cases were excluded.

There is in epidemiology and infectious disease a standard by which recommendations of this nature would be made, and that is something that most epidemiologists and infectious disease experts are familiar with called Koch's postulates. This states that, first of all, one wants to try to identify the agent believed to be responsible for the disease in a patient, then show that that agent can cause disease in either an animal model or a control patient, and then show that one can recover that agent from the animal model or the control patient. Then a fourth part of the postulate, which is not necessarily shown in all cases with Koch's postulates but should be in the case, is to show that removal or treatment of the presumed offending agent prevents the disease.

None of these, unfortunately, other than the first postulate, which was to identify a presumptive agent, have been fulfilled by this study.

I see a lot of problems with labeling precautions on aspirin. First of all, it is going to have a significant impact on physicians and on patients and parents, as you have already properly addressed. Physicians are likely to become medically legally culpable and be sued, because if they get a call in the middle of the night, as is the standard of practice of almost all family physicians and primary care physicians out in the real world of medicine, if they get a call in the middle of the night that a child is running a fever, is aching, is crying, is uncomfortable, the standard of care is to tell the mother to give the child aspirin, and if they child is not better in the morning, they will see the child. You know, that sounds like a joke, and many people make a joke of it, but that is the standard of care.

Mr. SCHEUER. In view of the concern and the research that has been done on this possible relationship of aspirin and Reye's syndrome, is that still the best advice that a patient could receive from a doctor in the middle of the night?

Dr. ORLOWSKI. I am not going to say it is the best advice, but it is certainly going to change, I am afraid. It is going to be compelled to change.

Mr. SCHEUER. Well, should it change?

Dr. ORLOWSKI. I don't think so, but I will address that in a minute.

Mr. SCHEUER. All right.

Dr. ORLOWSKI. Likewise, it is going to have a significant impact on parents, who are now going to feel that aspirin is a dangerous substance, and I will come back to comment on that in a minute, but I only wanted to comment that, as the FDA, I am sure, will concur, aspirin is the standard to which all other antipyretic or fever-treating drugs are compared. Aspirin is the standard throughout the world to which all other antipyretics are compared. So it is a very important drug, and I do not think anyone would deny that.

Likewise, my biggest concern, however, is that the implication—although the American Academy of Pediatrics redbook committee or committee on infectious disease was very careful not to make this type of recommendation, but unfortunately the CDC and apparently the FDA—the implication of their recommendation is that acetaminophen, or as we most know of it, Tylenol, is therefore safe. Aspirin is not safe, but acetaminophen is.

Having had an extensive amount of experience with both aspirin poisonings and acetaminophen poisonings, I will tell you, acetaminophen is a much more dangerous drug. It is insidious. The child looks fine after poisoning himself with acetaminophen, and the doctor can find nothing and frequently sends the child home only to have him present 3 or 4 days later, either in severe hepatic coma or frankly dead. Acetaminophen is an extremely dangerous drug in overdosage.

Aspirin poisoning we can treat, and the vast majority of aspirin poisonings, no matter how severe, can be handled appropriately in a pediatric intensive care unit and the child is saved. Acetaminophen, because of its insidious nature, we are not so lucky with, and there is an extensive amount of literature in the United Kingdom that shows that acetaminophen is an extremely dangerous drug.

This is my biggest concern. The American Academy of Pediatrics came out and said no antipyretics—sponging, you know, other measures to reduce fever but not using any drugs—but the recommendations that have been coming out, at least what I have heard from CDC and from the FDA, are a specific label on aspirin, therefore implying that the alternative, which almost everyone that watches TV or listens to the radio knows is Tylenol or acetaminophen, is therefore safe and aspirin is not, and that is very dangerous.

It is also going to prevent the proper study that should be done, a prospective study, and identification of the role of aspirin, possibly, in this syndrome from ever being done.

Likewise, as we have already heard, it is going to have a significant impact on other patients who must take aspirins such as, in pediatrics, the juvenile rheumatoid arthritis population, who in studies, as I understand it, have not been shown to have an increased incidence of Reye's syndrome despite taking aspirin daily for as long as they have the disease.

Likewise, Reye's syndrome is so rare, 1 to 2 cases per 100,000 children in the pediatric age group, that it seems that one needs to be a little more cautious about a recommendation of the magnitude

of what is being talked about here than in the case of a syndrome that would be much more common.

Influenza and chickenpox are very common childhood diseases. Aspirin is very commonly taken by pediatric patients. Yet Reye's syndrome is an extremely rare disease.

There is also a big difference, as has been pointed out by the individuals that came before me, between association and causality. This epidemiologic study implies that there may be an association, but it in no way indicates a causality or a cause and effect. But the problem is, no matter how nicely you word this in terms of the recommendations to the public, the public does not understand the difference between association and causality.

Mr. SCHEUER. Yes. Let me restate for the record that this morning when Dr. Brandt read his testimony, in every case where he used the word "association," where he said that the results of these studies indicate an association—this is just the first time, on page 1 of his testimony—he interlarded in his oral testimony, "the results of these studies tend to indicate an association," and he did that throughout. He must have gotten a sober second thought somewhere.

So he not only does not say causality; he doesn't even say now association. He talks about something that may tend to indicate an association. So that indicates, on his part, a very sober realization that he is walking on very thin ice.

Dr. ORLOWSKI. Yes, sir.

Mr. SCHEUER. But the actions, as I perceive them, of the Department, the action that they took when they finally bit the bullet and went from a standing to a walking posture, to me did not indicate that very respectful appreciation of how modest even the association is, let alone the causality. And, of course, it is this gap between the data base and the extent that they can prove even real association, let alone causality, and the action that they took, the far-reaching action that they took, which is at the basis of our concern.

Dr. ORLOWSKI. Well, just to emphasize my point, there is also an association between Reye's syndrome and attending school. There is an association between Reye's syndrome and being Caucasian. You have not seen any recommendations to change either one of those.

In conclusion, Mr. Chairman, I simply want to state that I personally give aspirin to my own son and at this stage will continue to do so. Thank you very much.

Mr. SCHEUER. Well, as I said the first day of hearings, my mother raised five children reasonably successfully and very healthily on two theorems: if there was something wrong on the outside, you put Vaseline on it; if there was something wrong on the inside, you stick a couple of aspirin down the throat. That worked pretty well, and I do not suppose you could develop a very much improved nostrum for just the general travails of childhood.

I would hate for that second nostrum, the aspirin, which seems to be proved and effective over many generations of kids, I would hate for that to be less available for parents in the overwhelming generality of cases where it seems to be effective and safe because, for an infinitesimal percentage of the patient population, there is

not a causality, not even an association, but something that might tend to indicate an association.

It seems to me, in terms of risks and benefits, we are taking an enormous risk with a very large population for a very speculative benefit to a very small population.

Dr. ORLOWSKI. I am afraid, sir, there are going to be others that are going to profit from this even more. I don't know if you are aware of the fact that acetaminophen is at least 5, if not 10, times more expensive than aspirin, which, if parents make this switch, which is going to be the public interpretation of the FDA recommendation, to go over to Tylenol, people are going to be spending a lot more money unnecessarily, and not necessarily safer, and I have to emphasize that again.

Mr. SCHEUER. Well, you testified before that acetaminophen is very much more dangerous.

Dr. ORLOWSKI. Absolutely. That is what I am saying.

Mr. SCHEUER. Acetaminophen poisoning—is that the right word?

Dr. ORLOWSKI. Yes, sir.

Mr. SCHEUER [continuing]. Is very much more insidious and very much less susceptible of identification, particularly by a doctor who is a general practitioner, I would think. Is that a reasonable statement?

Dr. ORLOWSKI. That is reasonable. I am not a general practitioner, but I think that is a reasonable statement.

Mr. SCHEUER. Congresswoman Schneider?

Mrs. SCHNEIDER. I am just curious if you could elaborate on some of the studies and observations similar to your own. Where might those be going on nationwide?

Dr. ORLOWSKI. In terms of the concern?

Mrs. SCHNEIDER. Well, in terms of the analysis and impact of the connection between aspirin and Reye's syndrome.

Dr. ORLOWSKI. I think the studies that have already been listed are the ones that have looked at the problem. I would be curious to know and, because of the time period, have not had the opportunity to communicate with some of my other colleagues in pediatric intensive care, to find out if the individuals in the State of Ohio experienced the same exclusion of their data that I did. Most pediatric intensive care units that see Reye's syndrome are going to see relatively small numbers in a year's time and not the magnitude of numbers that were listed in the Ohio Department of Health study, and I don't know whether they have met the same exclusion that I have, and I honestly don't know whether they have the same concerns about the probable lack of association, rather than probable association, between the drug and the syndrome.

Mrs. SCHNEIDER. I found your testimony very succinct and to the point. I do not have any other questions, Mr. Chairman.

Mr. SCHEUER. Thank you, Congresswoman Schneider.

Dr. Orłowski, are you familiar with a letter addressed to me dated the 28th of September from Dr. Thomas Halpin?

Dr. ORLOWSKI. I saw it for the first time this morning, sir.

Mr. SCHEUER. Without objection, I would like to have this letter entered into the record at this point.

[Letter referred to follows:]

240 N. High Street
Post Office Box 118
Columbus, Ohio 43216
Telephone (614) 464-3543



JAMES A. RHODES
Governor

JOHN M. ACKERMAN, M.D., M.P.H.
Director of Health

September 28, 1982

The Honorable James H. Scheuer
Chairman, Subcommittee on Natural Resources,
Agriculture Research and Environment
Suite 820
House Office Building
Annex #1
U. S. Capital
Washington, D. C. 20515

Attention: Mr. Jonah Shacknai

Dear Congressman Scheuer:

I appreciate the opportunity to enter this brief testimony for the September 28, 1982 Subcommittee hearing. I would like to add a special note of thanks to Mr. Jonah Shacknai for alerting us at the Ohio Department of Health to this subcommittee hearing. Unfortunately, I am not able to personally appear at this time due to a prior commitment, however, I will make every effort to appear at future subcommittee hearings if you so desire.

Between December 1978 and March 1980 the Ohio Department of Health carried out the largest case-control study on medication use and Reye's Syndrome ever conducted. During this time we had in place a very extensive surveillance system which I believe uncovered the vast majority of the cases of Reye's Syndrome that occurred during the study period. The heart of this system consisted of the six major pediatric referral centers in Ohio (Children's hospitals in Cleveland, Cincinnati, Columbus, Akron, Dayton and St. Vincent's Hospital in Toledo) which reported approximately 85% of our case reports; however, we received some case reports from 27 additional hospitals. All in all a total of 227 cases were reported to the Ohio Department of Health during the study period. Of these 227, 97 were used in the case control study and 94 of the 97 received a salicylate product. I would be happy to describe more details of the study at some future date; however, this information is contained in our recently published article in the Journal of the American Medical Association (JAMA 1982; 248:687-691).

I wanted to start off with this brief mention of our surveillance system to give the committee some indication of the large numbers of cases we were dealing with and because it has a bearing on the letter I recently received from Dr. James Orlowski of the Cleveland Clinic. There seems to have been a communication breakdown between

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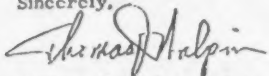
Dr. Orlowski and this Department. Of the patients he lists in his letter who could have been enrolled in the study (this would eliminate the three from 1981 since the study ended March 1980), we only have records of two cases being reported to the Ohio Department of Health or our Cleveland nurse coordinator (case BII and case TG). It's curious to me that we never encountered such reporting difficulties with the other 32 reporting hospitals.

I would like to take a few moments to describe the study process of the two cases actually reported to the Ohio Department of Health. As is our custom, I will refer to the cases by initials to protect the child's confidentiality even though Dr. Orlowski's previous communication with the aspirin company makes this a moot point. We found out about case H. H. about two weeks after he was admitted to Cleveland Clinic. H. H. was initially entered into the study, however, our nurse coordinator for the Cleveland area was not given access to his medical record and, therefore, H. H. could not be included in our study. At this point (July 1979) I wrote a letter to Dr. Orlowski requesting his cooperation with our Cleveland nurse coordinator. We did not hear of any additional cases from the Cleveland Clinic until March 1980. At that time T. G. was reported by Dr. Orlowski and enrolled in our study. Of the 64 Reye's Syndrome cases enrolled in the study from December 1979 through March 1980, T. G. was the only one without a history of salicylate ingestion even though he had a positive blood salicylate level. In addition, of the other 63 patients all (63 of 63) took aspirin before the onset of severe vomiting (i.e. the onset of Reye's Syndrome).

I am communicating the above information to Dr. Orlowski. I wish he would have contacted me first about his concerns before he contacted the Sterling Drug Company the previous week. From my point of view, I would think one might first contact the study director particularly since we reside in the same state.

In closing, I would like to compliment the U.S. Food and Drug Administration for their careful review of the Ohio study data and the Centers for Disease Control for their early assembly of an expert review panel. In particular, I would compliment Secretary Schweiker, Dr. Koop and Commissioner Hayes whose timely warnings have alerted the public to the salicylate-Reye's Syndrome link which may prevent some children from contracting this potentially devastating illness. On behalf of 3½ million Ohio children and their parents we are thankful.

Sincerely,



Thomas J. Halpin, M.D., M.P.H.
Chief, Bureau of Preventive Medicine

Mr. SCHEUER. Can I ask you some questions about that letter?

Dr. ORLOWSKI. Sure.

Mr. SCHEUER. He states in the letter that between December of 1978 and March of 1980, the Ohio Department of Health carried out a case-control study on medication used in Reye's syndrome, indicating they had a "very extensive surveillance system" which "uncovered the vast majority" of Reye's syndrome cases that occurred during the study period.

Does your experience as a participant in that study comport with Dr. Halpin's observation?

Dr. ORLOWSKI. Well, they did not need an extensive surveillance system in my particular aspect, sir, because I reported the cases to them, and so I think it raises questions about how the cases were excluded. I have no idea of how many cases they missed.

Mr. SCHEUER. Dr. Halpin states a communications breakdown, and those are his words, occurred between you and the Ohio Department of Health, and that they had records of only two cases being reported to the study. Are you aware of any reporting difficulties with the other cases referred to in your testimony?

Dr. ORLOWSKI. I am not. We used the protocol and the form that they gave us to fill out, and I don't understand where the breakdown did occur.

You heard a previous individual testify that they found a large number of our cases, in fact more than I was aware of, which is even possible, because I had no way of going back except by memory to pull out the cases that I found, so there may have been even more cases, which raises even more of a question about why so many of the cases were excluded.

Mr. SCHEUER. The chap from FDA this morning, I think, said that six cases were reported.

Dr. ORLOWSKI. He said he found 11 of my cases. I am not quite sure what he said about 6. But yes, they said they found 11 of my cases, apparently, in the exclusion data, at least if I am correct in interpreting what he said this morning.

Mr. SCHEUER. Well, then, how could Dr. Halpin have written that they had only a record of two cases?

Dr. ORLOWSKI. I don't know, sir. Again, this is the first time I saw this. I don't understand where the breakdown occurred. It obviously did not occur at my end.

Mr. SCHEUER. Were the cases cited by Dr. Halpin reported in a manner which comported with the study's protocols?

Dr. ORLOWSKI. Yes, sir. We were instructed, first of all, to report them to the Ohio Department of Health and then subsequently instructed to report them to a nurse clinician in the Cleveland area, who was responsible for doing the analysis in our particular area, and that is what we did.

Mr. SCHEUER. With respect to case B.H., Dr. Halpin states that the case was initially entered into the study, but as the nurse coordinator was not given access to the medical record, B.H. could not be ultimately included in the study. Is his assertion correct?

Dr. ORLOWSKI. If his implication is that we were the ones that denied access to the records, it makes no sense at all. Why would we bother to report the cases to the Ohio Department of Health and then not permit them to see the records? After all, we thought

we were participating in this study. So it makes no sense at all if his implication is that I was the one, or someone in my department, who was responsible for denying access. It is inconsistent.

Mr. SCHEUER. Did Dr. Halpin send you a letter seeking your cooperation with the study's nurse coordinator?

Dr. ORLOWSKI. I never saw the letter, sir.

Mr. SCHEUER. Were you aware of any criticism of your cooperation in this study prior to Dr. Halpin's letter to me?

Dr. ORLOWSKI. I had heard a verbal report within the last few days, and then for the first time in writing here, but never during the period of the study was any expression made to me of a lack of cooperation.

Mr. SCHEUER. Either orally or in writing?

Dr. ORLOWSKI. No, sir.

Mr. SCHEUER. Dr. Halpin appears to note some inconsistency between your report that patient T.G. had no history of salicylate ingestion, yet had a positive blood salicylate level. Are those two findings inconsistent?

Dr. ORLOWSKI. No, sir.

Mr. SCHEUER. Or incompatible.

Dr. ORLOWSKI. It is a well-known fact that individuals who are very sick with Reye's syndrome, especially in the early stages, have what we call ketoacidosis. The ketones that are in the blood interfere with the assay method that is predominantly used in the country for assaying for salicylates. And so there is an interference, and because the patient had no history of salicylate ingestion or products containing salicylates and *BAD MAG TAPE**ERR01* had an extremely low blood level which was compatible with ketone interference with the test, that was how we interpreted it.

Interestingly enough, it is individuals from Ohio that have recently reported this phenomenon in the medical literature, that it is in fact ketone interference that gives low salicylate levels or gives false positives, as we call them, on salicylate determinations. In fact, it is individuals that were at institutions that were participating in the Ohio Department of Health study.

Mr. SCHEUER. Our counsel?

Mr. SHACKNAI. Dr. Orlowski, there is an implication in this letter from Dr. Halpin that rather than contacting him with your concern about discrepancies in the data, instead, according to this letter, you went ahead and contacted an aspirin company. Is that an accurate representation of the chain of events?

Dr. ORLOWSKI. No, sir, it is not. What happened was that, over the last 8 to 10 months, I have been quoted at least three times in the medical press as having stated that I felt that the data were at best tenuous and insufficient to make the degree of recommendations that were being made.

I was also quoted at some medical meetings at which I spoke on the subject as saying that I personally did not feel that the association was strong enough at this time to recommend that parents not give aspirin to children with flu-like symptoms or varicella.

This apparently was seen by a representative of one of the pharmaceutical companies who approached me—at the time I did not know who he was, nor did I know who—I knew the name of the drug company that he represented but did not know that that par-

ticular drug company was responsible for marketing aspirin, because, as most individuals are probably unaware, the name that goes on the common brands of aspirin has absolutely nothing to do with the drug company, and I also was completely in the dark about the fact that this drug company was an aspirin producer.

That individual asked me, on the basis of the quotations that had appeared in medical press articles about me, as to what my feelings were, and I told him the same thing that I have stated at meetings. He then asked me if I was willing to pursue this further, and I told him that I had been in the process of getting together data to question Dr. Halpin about why there was the inconsistency between what he reported in the Journal of the American Medical Association and the cases that I had submitted to him. And so I went ahead with that and, out of courtesy, copied it to the drug company.

Mr. SHACKNAL. So, in other words, they contacted you rather than, as Dr. Halpin represents, your contacting them?

Dr. ORLOWSKI. Yes, sir. I never contacted them. No, sir.

Mr. SHACKNAL. Thank you, Mr. Chairman.

Mr. SCHEUER. Do you have any final remarks to make?

Dr. ORLOWSKI. No, sir. I have made them.

Mr. SCHEUER. All right. Thank you very, very much, Dr. Orlofski. We are very grateful for your testimony.

This completes our testimony for the day, and we will reconvene subject to the call of the Chair.

[Whereupon, at 11:46 a.m., the subcommittee recessed, to reconvene at the call of the Chair.]

